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NEWS 4	Feb 16	TOXLINE no longer being updated
NEWS 5	Apr 23	Search Derwent WPINDEX by chemical structure
NEWS 6	Apr 23	PRE-1967 REFERENCES NOW SEARCHABLE IN CAPLUS AND CA
NEWS 7	May 07	DGENE Reload
NEWS 8	Jun 20	Published patent applications (A1) are now in USPATFULL
NEWS 9	JUL 13	New SDI alert frequency now available in Derwent's DWPI and DPCI
NEWS 10	Aug 23	In-process records and more frequent updates now in MEDLINE
NEWS 11	Aug 23	PAGE IMAGES FOR 1947-1966 RECORDS IN CAPLUS AND CA
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NEWS 14	Oct 09	Korean abstracts now included in Derwent World Patents Index
NEWS 15	Oct 09	Number of Derwent World Patents Index updates increased
NEWS 16	Oct 15	Calculated properties now in the REGISTRY/ZREGISTRY File
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NEWS 19	Oct 29	AAASD no longer available

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=> s (nucl;ear (a) receptor) ligand (p) screen? (p) reporter

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The number of right parentheses in a query must be equal to the
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=> s (nuclear (a) receptor) ligand (p) screen? (p) reporter

MISSING OPERATOR RECEPTOR) LIGAND
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s (nuclear (a) receptor)(p) ligand (p) screen? (p) reporter

L1          75 (NUCLEAR (A) RECEPTOR)(P) LIGAND (P) SCREEN? (P) REPORTER

=> dup rem l1

PROCESSING COMPLETED FOR L1
L2           34 DUP REM L1 (41 DUPLICATES REMOVED)

=> s (nuclear (a) receptor)(p) gene (p) screen? (p) reporter

   4 FILES SEARCHED...
L3          80 (NUCLEAR (A) RECEPTOR)(P) GENE (P) SCREEN? (P) REPORTER

=> dup rem l3

PROCESSING COMPLETED FOR L3
L4           35 DUP REM L3 (45 DUPLICATES REMOVED)

=> s l2 and l4

L5          27 L2 AND L4

=> dup rem l5
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PROCESSING COMPLETED FOR L5
L6 27 DUP REM L5 (0 DUPLICATES REMOVED)

=> s l2 or l4

L7 42 L2 OR L4

=> dup rem l7

PROCESSING COMPLETED FOR L7
L8 42 DUP REM L7 (0 DUPLICATES REMOVED)

=> d l8 total ibib kwic

L8 ANSWER 1 OF 42 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:618285 CAPLUS
DOCUMENT NUMBER: 135:176717
TITLE: A ligand dependent nuclear receptors transactivation system for screening insecticidal compds
INVENTOR(S): Tran, Hiep Tuan; Askari, Hossein; Schwartz, Michael; Butt, Tauseef
PATENT ASSIGNEE(S): Lifesensors, Inc., USA
SOURCE: PCT Int. Appl., 84 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001061350	A1	20010823	WO 2001-US5429	20010220

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-183393 P 20000218
REFERENCE COUNT: 6
REFERENCE(S):
(1) Dela, C; Journal of Molecular Endocrinology 2000, V24, P183
(2) Evans; US 5747661 A 1998 CAPLUS
(3) Heinrich; US 6110698 A 2000 CAPLUS
(4) Torchia, J; Nature 1997, V387, P677 CAPLUS
(6) Wang, S; The Journal of Biological Chemistry 1998, V273(42), P27531 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB A yeast-based system is provided for identifying new mols. which activate **nuclear receptors** in a **ligand**-dependent fashion. A **ligand** dependent transactivation system for **screening** insecticidal compds. comprises: (a) a first DNA construct having a nucleic acid mol. encoding an altered ecdysone receptor operably linked to a promoter; (b) a second DNA construct having a nucleic acid mol. encoding a receptor, which heterodimerizes with said ecdysone receptor upon transactivation, said nucleic acid being operably linked to a promoter; (c) a third DNA construct comprising a promoter contg. a plurality of ecdysone response elements, said promoter being operably linked to a **reporter gene**; (d) a fourth DNA construct

encoding a co-activator mol., said co-activator mol. being operably linked to a promoter sequence; and (e) a host cell comprising said first, second, third and fourth DNA constructs, expression of said **reporter gene** being dependent upon **ligand** dependent transactivation effectuated by said insecticidal compds. In a preferred embodiment, a method is provided utilizing ecdysone receptor, USP and GRIP I encoding expression vectors which may be used to advantage for **screening** new and useful insecticidal compds., detecting insecticidal residues as well as to regulate expression of a **gene** of interest in a host in a **ligand**-dependent manner.

IT Ecdysteroid receptors
Nuclear receptors
Promoter (genetic element)
Reporter gene
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(**ligand** dependent **nuclear receptors** transactivation system for **screening** insecticidal compds comprising)

L8 ANSWER 2 OF 42 USPATFULL

ACCESSION NUMBER:	2001:190920 USPATFULL
TITLE:	Use of modified tethers in screening compound libraries
INVENTOR(S):	Dower, William J., Menlo Park, CA, United States Gates, Christian M., Santa Cruz, CA, United States Heinkel, Gregory L., San Jose, CA, United States Lalonde, Guy, Woodside, CA, United States Mattheakis, Larry C., Cupertino, CA, United States Paddon, Christopher J., Pacifica, CA, United States Schatz, Peter J., Mountain View, CA, United States
PATENT ASSIGNEE(S):	Glaxo Wellcome Inc., Research Triangle Park, NC, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6309842	B1	20011030
APPLICATION INFO.:	US 1997-977378		19971124 (8)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1996-758307, filed on 3 Dec 1996, now patented, Pat. No. US 5958703		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	GRANTED		
PRIMARY EXAMINER:	Ponnaluri, Padmashri		
LEGAL REPRESENTATIVE:	Townsend & Townsend & Crew		
NUMBER OF CLAIMS:	4		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	14 Drawing Figure(s); 13 Drawing Page(s)		
LINE COUNT:	3151		

DETD The regulatory sequences depend on the target receptor. For example, to **screen** for activators of 7TM receptors, the recombinase is placed under the transcriptional control of a promoter which responds to 7TM. . . . promoter composed of repeating cyclic AMP response elements, or the Fusl promoter if the 7TM receptor is expressed in yeast **reporter** cells. As a further example, to **screen** for activation of a T-cell receptor, the recombinase can be linked to an NFAT promoter. In a further variation, the. . . . target receptor, such that the recombinase is inactive in the fusion protein unless the fusion protein is bound to a **ligand**, which causes steric changes that

activate the recombinase. Activation of recombinases fused to **ligand** binding domains of **nuclear receptors** on **ligand** binding has been reported. See Logie & Stewart, Proc. Natl. Acad. Sci. USA 92, 5940-5944 (1995); Metzger et al., Proc. Natl. Acad. Sci. USA 92, 6991-6995 (1995); U.S. Ser. No. 08/901,540. Suitable **nuclear receptors** include estrogen, glucocorticoid and androgen receptors.

L8 ANSWER 3 OF 42 USPATFULL

ACCESSION NUMBER: 2001:67659 USPATFULL

TITLE: Synthesis and use of retinoid compounds having negative hormone and/or antagonist activities

INVENTOR(S): Klein, Elliott S., Marina del Rey, CA, United States
Johnson, Alan T., Rancho Santa Margarita, CA, United States
Standeven, Andrew M., Corona del Mar, CA, United States
Beard, Richard L., Newport Beach, CA, United States
Gillett, Samuel J., Albany, CA, United States
Duong, Tien T., Irvine, CA, United States
Nagpal, Sunil, Lake Forest, CA, United States
Vuligonda, Vidyasagar, Irvine, CA, United States
Teng, Min, Aliso Viejo, CA, United States
Chandraratna, Roshantha A., Mission Viejo, CA, United States

PATENT ASSIGNEE(S): Allergan, Inc., Irvine, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6228848	B1	20010508
APPLICATION INFO.:	US 1999-447082		19991122 (9)

RELATED APPLN. INFO.: Division of Ser. No. US 1998-222983, filed on 30 Dec 1998, now patented, Pat. No. US 6008204 Division of Ser. No. US 1997-871093, filed on 9 Jun 1997, now patented, Pat. No. US 5952345 Division of Ser. No. US 1996-613863, filed on 11 Mar 1996, now patented, Pat. No. US 5776699 And Ser. No. US 1995-522778, filed on 1 Sep 1995 And Ser. No. US 1995-522779, filed on 1 Sep 1995

	NUMBER	DATE
PRIORITY INFORMATION:	US 1995-19015	19950901 (60)
	US 1995-64853	19951013 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Shah, Mukund J.
ASSISTANT EXAMINER: Rao, Deepak R.
LEGAL REPRESENTATIVE: Szekeres, Gabor L., Baran, Robert J., Voet, Martin A.
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 30 Drawing Figure(s); 15 Drawing Page(s)
LINE COUNT: 6462
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD Our method of RAR negative hormone **screening** based on the use of CV-1 cells co-transfected with the ERE-tk-Luc luciferase **reporter** plasmid and the ER-RXR-.alpha. and RAR-.gamma.-VP-16 receptor expression plasmids can be adapted generally such that the RAR-.gamma. moiety of the. . . to that of peroxisome proliferator-activated receptors (PPAR), vitamin D receptor (VDR), thyroid hormone receptor (T3R) or any other steroid superfamily **nuclear receptor** capable of heterodimerizing with RXR. CV-1 cells co-transfected with such plasmids would express high basal levels of luciferase activity. **Ligands** capable of binding the

ligand binding domain of the receptor substituted for the RAR-.gamma. moiety can be easily **screened** for negative hormone activity by measuring their ability to repress luciferase activity.

DETD For steroid superfamily **nuclear receptors** that do not heterodimerize with RXR (e.g., glucocorticoid and estrogen receptors) the same end result can be achieved using GR-VP-16 or ER-VP-16 receptors and a luciferase **reporter** plasmid consisting of the appropriate glucocorticoid or estrogen response element fused to a heterologous promoter element and luciferase or other **reporter gene**. An essential feature of a generalized negative hormone **screening** assay is the inclusion of at least the **ligand** binding domain of the particular **nuclear receptor** for which inverse agonists are to be **screened** and a method for localizing the **nuclear receptor ligand** binding domain to the promoter of a **reporter gene**. This could be achieved using the receptors's natural DNA binding site, or alternatively by construction of a chimeric receptor having a heterologous DNA binding domain and corresponding use of a **reporter gene** which is under control of a DNA regulatory element which is recognized by the heterologous DNA binding domain. In a preferred embodiment, the plasmid expressing the **nuclear receptor** for which inverse agonists are to be **screened** would express this **nuclear receptor** as a fusion protein containing a constitutive activation domain, such as the HSV VP-16 activation domain, in order to provide allow high basal activity. This high basal activity would effectively increase assay sensitivity, thereby allowing analysis of **nuclear receptor ligands** which repress basal transcriptional activity in the absence of added **nuclear receptor** agonist.

L8 ANSWER 4 OF 42 USPATFULL

ACCESSION NUMBER:	2001:55705 USPATFULL
TITLE:	Methods of identifying compounds having nuclear receptor negative hormone and/or antagonist activities
INVENTOR(S):	Klein, Elliott S., Marina Del Rey, CA, United States Nagpal, Sunil, Lake Forest, CA, United States Chandraratna, Roshantha A., Mission Viejo, CA, United States
PATENT ASSIGNEE(S):	Allergan Sales, Inc., Irvine, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6218128	B1	20010417
APPLICATION INFO.:	US 1998-42943		19980317 (9)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1997-928552, filed on 12 Sep 1997, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Ulm, John		
LEGAL REPRESENTATIVE:	Fisher, Carlos A., Baran, Robert J., Voet, Martin A.		
NUMBER OF CLAIMS:	21		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	30 Drawing Figure(s); 20 Drawing Page(s)		
LINE COUNT:	7525		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD Our method of RAR negative hormone **screening** based on the use of CV-1 cells co-transfected with the ERE-tk-Luc luciferase **reporter** plasmid and the ER-RXR-.alpha. and RAR-.gamma.-VP-16 receptor expression plasmids can be adapted generally such that the RAR-.gamma. moiety of the. . . to that of peroxisome proliferator-activated receptors (PPAR), vitamin D receptor (VDR), thyroid hormone receptor (T3R) or any other steroid superfamily

nuclear receptor capable of heterodimerizing with RXR. CV-1 cells co-transfected with such plasmids would express high basal levels of luciferase activity. **Ligands** capable of binding the **ligand** binding domain of the receptor substituted for the RAR-.gamma. moiety can be easily **screened** for negative hormone activity by measuring their ability to repress luciferase activity.

DETD For steroid superfamily **nuclear receptors** that do not heterodimerize with RXR (e.g., glucocorticoid and estrogen receptors) the same end result can be achieved using GR-VP-16 or ER-VP-16 receptors and a luciferase **reporter** plasmid consisting of the appropriate glucocorticoid or estrogen response element fused to a heterologous promoter element and luciferase or other **reporter gene**. An essential feature of a generalized negative hormone **screening** assay is the inclusion of at least the **ligand** binding domain of the particular **nuclear receptor** for which inverse agonists are to be **screened** and a method for localizing the **nuclear receptor ligand** binding domain to the promoter of a **reporter gene**. This could be achieved using the receptors's natural DNA binding site, or alternatively by construction of a chimeric receptor having a heterologous DNA binding domain and corresponding use of a **reporter gene** which is under control of a DNA regulatory element which is recognized by the heterologous DNA binding domain. In a preferred embodiment, the plasmid expressing the **nuclear receptor** for which inverse agonists are to be **screened** would express this **nuclear receptor** as a fusion protein containing a constitutive activation domain, such as the HSV VP-16 activation domain, in order to provide allow high basal activity. This high basal activity would effectively increase assay sensitivity, thereby allowing analysis of **nuclear receptor ligands** which repress basal transcriptional activity in the absence of added **nuclear receptor** agonist.

L8 ANSWER 5 OF 42 USPATFULL

ACCESSION NUMBER:	2001:18502 USPATFULL
TITLE:	Methods and compositions for use in modulating expression of matrix metalloproteinase genes
INVENTOR(S):	Basset, Paul, Strasbourg, France Anglard, Patrick, Strasbourg, France Guerin, Eric, Strasbourg, France
PATENT ASSIGNEE(S):	Institut National de la Sante de la Recherche Medicale, Paris, France (non-U.S. corporation) Centre National de la Recherche Scientifique, Paris, France (non-U.S. corporation) Universite Louis Pasteur, Strasbourg, France (non-U.S. corporation) Bristol-Myers Squibb Company, Princeton, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6184256	B1	20010206
APPLICATION INFO.:	US 1998-65904		19980424 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-44258	19970424 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Schwartzman, Robert A.
LEGAL REPRESENTATIVE:	Sterne, Kessler, Goldstein & Fox, P.L.L.C.
NUMBER OF CLAIMS:	23

EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 10 Drawing Figure(s); 10 Drawing Page(s)
LINE COUNT: 2099
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . more of the compositions to be assayed for its ability to differentially modulate the expression of the two or more **genes** in the cell, while the second mammalian cell is incubated in parallel with the first cell but in the absence. . . the second mammalian cell

serves as a "control" cell to indicate the levels of expression of the two or more **genes** typically seen in that particular cell type in the absence of the compositions to be assayed, and provides a reference for determining the effects of the compositions on **gene** expression. As an alternative to using normal, diseased or established cells, transfected cell lines may be constructed and used in

the methods of the invention. For example, in Chen et al., EMBO J. 14(6):1187-1197 (1995), three `**reporter**` cell lines have been used to characterize a number of RAR.alpha.-, RAR.beta.-, or RAR.gamma.-specific dissociating synthetic retinoids that selectively induce the AF-2 activation function present in the **ligand** -binding domain (LBD) of RAR.beta. (.beta.AF-2). These cell lines stably

express chimeric proteins containing the DNA binding domain of the yeast. . . (which contain that LBD and the AF-2 activation function) of RAR.alpha. (GAL-RAR.alpha.), RAR.beta. (GAL-RAR.beta.) or RAR.gamma. (GAL-RAR.gamma.), and a luciferase **reporter gene** driven by a pentamer of the GAL4 recognition sequence ("17 m") in front of the .beta.-globin promoter (17 m) 5-GAL-Luc). In these cell lines, the RAR **ligands** thus induce luciferase activity that can be measured in.the intact cells using a single-photon-counting camera. This

reporter system is insensitive to endogenous receptors which cannot recognize the GAL4 binding site. Using analogous **screening** assays, these synthetic retinoids, like RA, have been reported to inhibit the anchorage-independent growth of oncogene-transformed 3T3 cells, while the promoter of the human interleukin-6 (IL-6) **gene**, whose product is involved in the regulation of hematopoiesis, immune responses and inflammation (Kishimoto, T. et al., Science 258:593-597 (1992)),. . . a similar manner, RXR agonists have been identified using cell lines that express a RXR receptor linked to a TREpal-tk **reporter gene** which is activated by both RAR-RXR heterodimers and RXR homodimers (Lehmann, J. M., et al., Science 258:1944-1946 (1992)). Thus, **reporter** cell lines that are easily constructed, by methods routine to one of ordinary skill, may be used to distinguish not only the specific RAR or RXR types to which a candidate **ligand** will bind, but also whether that binding induces an activating or inhibiting (i.e., agonistic or antagonistic) effect. Although the above-referenced **reporter** cell lines comprised the luciferase or thymidine kinase **genes** as **reporters**, other **reporters** such as Neo, CAT, .beta.-galactosidase or Green Fluorescent Protein are well known in the art and may be used in a similar fashion to carry our the present invention. For example, the use of CAT **reporters** to measure retinoic acid inhibition of stromelysin-1 **gene** expression has been reported (Nicholson, R. C., et al., EMBO J. 9(13):4443-4454 (1990)), and CAT **reporters** have been used in the methods of the present invention to examine RAR and RXR modulation of MMP **gene** expression, particularly of stromelysin-3 **gene** expression, as shown below in Example 4. Other references disclosing **reporter** plasmids containing a **reporter** **gene** and expression vectors encoding a LBD of a **nuclear** **receptor** include Meyer et al., Cell 57:433-442 (1989); Meyer et al., EMBO J. 9(12):3923-3932 (1990); Tasset et al., Cell 62:1177-1187 (1990);. . .

L8 ANSWER 6 OF 42 MEDLINE
ACCESSION NUMBER: 2001409905 MEDLINE
DOCUMENT NUMBER: 21197982 PubMed ID: 11301062
TITLE: Binding of prostaglandins to human PPARgamma: tool assessment and new natural ligands.
AUTHOR: Ferry G; Bruneau V; Beauverger P; Goussard M; Rodriguez M; Lamamy V; Dromaint S; Canet E; Galizzi J P; Boutin J A
CORPORATE SOURCE: Division de Pharmacologie Moleculaire et Cellulaire, Institut de Recherches Servier, 125 Chemin de Ronde, 78 290, Croissy-sur-Seine, France.
SOURCE: EUROPEAN JOURNAL OF PHARMACOLOGY, (2001 Apr 6) 417 (1-2) 77-89.
Journal code: EN6; 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010723
Last Updated on STN: 20010723
Entered Medline: 20010719

AB The peroxisome proliferator-activated receptors (PPAR) form a family of **nuclear receptors** with a wide variety of biological roles from adipogenesis to carcinogenesis. More **ligands** (agonist and antagonist) are needed to explore the multiple functions of PPAR, particularly PPARgamma. In order to complete such **ligand screening**, a binding test should be assessed versus the classical transactivation **reporter gene** assay. In the present work, the full-length human PPARgamma protein as well as its **ligand** binding domain portion were expressed in Escherichia coli. Bacterial membrane preparations expressing those constructs were characterized using a classical binding. . . measured with a new alternative method. The systems were assessed using a series of reference PPAR (alpha, beta and gamma) **ligands**. The full-length human PPARgamma fused to glutathione-S-transferase, expressed in E. coli and tested as a bacterial membrane-bound protein led to. . . the most accurate results when compared to the literature. Furthermore, in an attempt to complete the panel of natural PPARgamma **ligands**, 29 commercially available prostaglandins were **screened** in the binding assay. Prostaglandins H(1) and H(2) were found to be modest **ligands**, however as potent as 15Delta(12-14)prostaglandin J(2). These results were confirmed in the classical transactivation assay. The fact that these three prostaglandins were equally potent, suggests new pathways of PPARgamma-linked **gene** activation.

L8 ANSWER 7 OF 42 USPATFULL
ACCESSION NUMBER: 2000:134897 USPATFULL
TITLE: Therapeutic combinations of RAR antagonists and RXR agonists and use thereof
INVENTOR(S): Chambon, Pierre, Blaesheim, France
Gronemeyer, Hinrich, Oberkirch, Germany, Federal Republic of
Reczek, Peter R., East Amherst, NY, United States
Ostrowski, Jacek, Getzville, NY, United States
PATENT ASSIGNEE(S): Institut National de la Sante et de la Recherche Medicale, Paris, France (non-U.S. corporation)
Centre National de la Recherche Scientifiques, Paris, France (non-U.S. corporation)
Universite Louis Pasteur, Straasbourg, France (non-U.S. corporation)
Bristols-Myers Squibb Company, Princeton, NJ, United States (U.S. corporation)

NUMBER	KIND	DATE

PATENT INFORMATION: US 6130230 20001010
APPLICATION INFO.: US 1997-919318 19970828 (8)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1996-24772	19960828 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Jones, Dwayne C.
LEGAL REPRESENTATIVE: Sterne, Kessler Goldstein & Fox, P.L.L.C.
NUMBER OF CLAIMS: 38
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Figure(s); 9 Drawing Page(s)
LINE COUNT: 1818
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD A number of methods for **screening** candidate RAR antagonists and RXR agonists, generated by rational design or computer modeling as described above, are well-known in the. . . is useful in the methods of the present invention. For example, in Chen et al., EMBO J. 14(6):1187-1197 (1995), three `**reporter**` cell lines have been used to characterize a number of RAR.alpha.-, RAR.beta.-, or RAR.gamma.-specific dissociating synthetic retinoids that selectively induce. . . (which contain that LBD and the AF-2 activation function) of RAR.alpha. (GAL-RAR.alpha.), RAR.beta. (GAL-RAR.beta.) or RAR.gamma. (GAL-RAR.gamma.), and a luciferase **reporter gene** driven by a pentamer of the GAL4 recognition sequence (`17m`) in front of the .beta.-globin promoter (17m)5-GAL-Luc). In these cell lines, the RAR **ligands** thus induce luciferase activity that can be measured in the intact cells using a single-photon-counting camera. This **reporter** system is insensitive to endogenous receptors which cannot recognize the GAL4 binding site. Using analogous **screening** assays, these synthetic retinoids, like RA, have been reported to inhibit the anchorage-independent growth of oncogene-transformed 3T3 cells, while the promoter of the human interleukin-6 (IL-6) **gene**, whose product is involved in the regulation of hematopoiesis, immune responses and inflammation (Kishimoto, T. et al., Science 258:593-597 (1992)),. . . a similar manner, RXR agonists have been identified using cell lines that express a RXR receptor linked to a TREpal-tk **reporter gene** which is activated by both RAR-RXR heterodimers and RXR homodimers (Lehmann, J. M., et al., Science 258:1944-1946 (1992)). Thus, **reporter** cell lines that are easily constructed, by methods routine to one of ordinary skill, may be used to distinguish not only the specific RAR or RXR types to which a candidate **ligand** will bind, but also whether that binding induces an activating (i.e., agonistic) or repressive (i.e., antagonistic) effect. Although the above-referenced **reporter** cell lines comprised the luciferase or thymidine kinase **genes** as **reporters**, other **reporters** such as Neo, CAT, .beta.-galactosidase or Green Fluorescent Protein are well known in the art and may be used in a similar fashion to carry out the present invention. For example, references disclosing **reporter** plasmids containing a **reporter gene** and expression vectors encoding a LBD of a **nuclear receptor** include Meyer et al., Cell 57:433-442 (1989); Meyer et al., EMBO J. 9(12):3923-3932 (1990); Tasset et al., Cell 62:1177-1187 (1990);. . .

L8 ANSWER 8 OF 42 USPATFULL
ACCESSION NUMBER: 2000:121281 USPATFULL
TITLE: Methods to screen for transcription factor-coactivator interactions
INVENTOR(S): Kushner, Peter J., San Francisco, CA, United States
Webb, Paul, San Francisco, CA, United States
Uht, Rosalie M., San Francisco, CA, United States

PATENT ASSIGNEE(S): The Regents of the University of California, Oakland, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6117638		20000912
APPLICATION INFO.:	US 1998-54238		19980402 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-43059	19970404 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: McKelvey, Terry
LEGAL REPRESENTATIVE: Skjerven, Morrill, MacPherson, Franklin & Friel, LLP, Hunter, Esq., Tom
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 15 Drawing Figure(s); 10 Drawing Page(s)
LINE COUNT: 1364
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD The invention also provides methods for identifying previously unknown coactivators that are involved in **nuclear receptor** -mediated transcriptional regulation. An expression library of cDNA molecules is prepared from mRNA obtained from a cell in which a **gene** of interest is expressed. Expression **screening** is described in, for example, Ausubel, supra. The expression vector used for the library includes a DNA binding domain coding. . . a host cell with a transcription factor polypeptide, which can also be provided by means of expression of a heterologous **gene**. A hormone or analog that binds to the transcription factor polypeptide is also introduced into the cells, thus activating the transcription factor polypeptide. In a preferred embodiment, the host cells also contain a **reporter gene** that is operably linked to a response element that corresponds to the DNA binding domain encoded by the expression vector. Clones that encode an activation domain of a coactivator will trigger expression of **genes** that are operably linked to the response element.

L8 ANSWER 9 OF 42 USPATFULL
ACCESSION NUMBER: 2000:91965 USPATFULL
TITLE: Synthesis and use of retinoid compounds having negative hormone and/or antagonist activities
INVENTOR(S): Klein, Elliott S., Marina del Rey, CA, United States
Johnson, Alan T., Rancho Santa Margarita, CA, United States
Standeven, Andrew M., Corona del Mar, CA, United States
Beard, Richard L., Newport Beach, CA, United States
Gillett, Samuel J., Albany, CA, United States
Duong, Tien T., Irvine, CA, United States
Nagpal, Sunil, Lake Forest, CA, United States
Vuligonda, Vidyasagar, Irvine, CA, United States
Teng, Min, Aliso Viejo, CA, United States
Chandraratna, Roshantha A., Mission Viejo, CA, United States
PATENT ASSIGNEE(S): Allergan Sales, Inc., Irvine, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6090810		20000718
APPLICATION INFO.:	US 1998-222984		19981230 (9)

RELATED APPLN. INFO.: Division of Ser. No. US 1997-871093, filed on 9 Jun

1997, now patented, Pat. No. US 5952345 which is a division of Ser. No. US 1996-613863, filed on 11 Mar 1996, now patented, Pat. No. US 5776699

	NUMBER	DATE
PRIORITY INFORMATION:	US 1995-19015	19950901 (60)
	US 1995-64853	19951013 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Raymond, Richard L.
ASSISTANT EXAMINER: Rao, Deepak R.
LEGAL REPRESENTATIVE: Szekeres, Gabor L., Baran, Robert J., Voet, Martin A.
NUMBER OF CLAIMS: 38
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 20 Drawing Figure(s); 15 Drawing Page(s)
LINE COUNT: 7116
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD Our method of RAR negative hormone **screening** based on the use of CV-1 cells co-transfected with the ERE-tk-Luc luciferase **reporter** plasmid and the ER-RXR-.alpha. and RAR-.gamma.-VP-16 receptor expression plasmids can be adapted generally such that the RAR-.gamma. moiety of the. . . to that of peroxisome proliferator-activated receptors (PPAR), vitamin D receptor (VDR), thyroid hormone receptor (T3R) or any other steroid superfamily **nuclear receptor** capable of heterodimerizing with RXR. CV-1 cells co-transfected with such plasmids would express high basal levels of luciferase activity. **Ligands** capable of binding the **ligand** binding domain of the receptor substituted for the RAR-.gamma. moiety can be easily **screened** for negative hormone activity by measuring their ability to repress luciferase activity.

DETD For steroid superfamily **nuclear receptors** that do not heterodimerize with RXR (e.g., glucocorticoid and estrogen receptors) the same end result can be achieved using GR-VP-16 or ER-VP-16 receptors and a luciferase **reporter** plasmid consisting of the appropriate glucocorticoid or estrogen response element fused to a heterologous promoter element and luciferase or other **reporter gene**. An essential feature of a generalized negative hormone **screening** assay is the inclusion of at least the **ligand** binding domain of the particular **nuclear receptor** for which inverse agonists are to be **screened** and a method for localizing the **nuclear receptor ligand** binding domain to the promoter of a **reporter gene**. This could be achieved using the receptors's natural DNA binding site, or alternatively by construction of a chimeric receptor having a heterologous DNA binding domain and corresponding use of a **reporter gene** which is under control of a DNA regulatory element which is recognized by the heterologous DNA binding domain. In a preferred embodiment, the plasmid expressing the **nuclear receptor** for which inverse agonists are to be **screened** would express this **nuclear receptor** as a fusion protein containing a constitutive activation domain, such as the HSV VP-16 activation domain, in order to provide allow high basal activity. This high basal activity would effectively increase assay sensitivity, thereby allowing analysis of **nuclear receptor ligands** which repress basal transcriptional activity in the absence of added **nuclear receptor** agonist.

L8 ANSWER 10 OF 42 MEDLINE
ACCESSION NUMBER: 2000136063 MEDLINE
DOCUMENT NUMBER: 20136063 PubMed ID: 10669760
TITLE: Mouse Zac1, a transcriptional coactivator and repressor for

nuclear receptors.
AUTHOR: Huang S M; Stallcup M R
CORPORATE SOURCE: Departments of Pathology and of Biochemistry and Molecular Biology, University of Southern California, Los Angeles, California 90089, USA.
CONTRACT NUMBER: DK 55274 (NIDDK)
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 Mar) 20 (5) 1855-67. Journal code: NGY; 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000327
Last Updated on STN: 20000327
Entered Medline: 20000316

AB Transcriptional activation by nuclear hormone receptors is mediated by the 160-kDa family of **nuclear receptor** coactivators. These coactivators associate with DNA-bound **nuclear receptors** and transmit activating signals to the transcription machinery through two activation domains. In **screening** for mammalian proteins that bind the C-terminal activation domain of the **nuclear receptor** coactivator GRIP1, we identified a new variant of mouse Zac1 which we call mZac1b. Zac1 was previously discovered as a. . . yeast two-hybrid assays and in vitro, mZac1b bound to GRIP1, to CREB-binding protein (CBP) and p300 (which are coactivators for **nuclear receptors** and other transcriptional activators), and to **nuclear receptors** themselves in a hormone-independent manner. In transient-transfection assays mZac1b exhibited a transcriptional activation activity when fused with the Gal4 DNA. . . binding domain fused to GRIP1 or CBP fragments. More importantly, mZac1b was a powerful coactivator for the hormone-dependent activity of **nuclear receptors**, including androgen, estrogen, glucocorticoid, and thyroid hormone receptors. However, with some **reporter genes** and in some cell lines mZac1b acted as a repressor rather than a coactivator of **nuclear receptor** activity. Thus, mZac1b can interact with **nuclear receptors** and their coactivators and play both positive and negative roles in regulating **nuclear receptor** function.

L8 ANSWER 11 OF 42 MEDLINE
ACCESSION NUMBER: 2000158851 MEDLINE
DOCUMENT NUMBER: 20158851 PubMed ID: 10692587
TITLE: Cloning of a mouse glucocorticoid modulatory element binding protein, a new member of the KDWK family.
AUTHOR: Jimenez-Lara A M; Heine M J; Gronemeyer H
CORPORATE SOURCE: Institut de Genetique et de Biologie Moleculaire et Cellulaire, CNRS/INSERM/ULP, P.O. Box 163, 67404, Illkirch, France.
SOURCE: FEBS LETTERS, (2000 Feb 25) 468 (2-3) 203-10. Journal code: EUH; 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000413
Last Updated on STN: 20000413
Entered Medline: 20000403

AB A mouse cDNA that encodes a nuclear DNA binding protein was identified by yeast two-hybrid **screening** using the activation domain 2 of the **nuclear receptor** coactivator TIF2 as a bait. BLAST

analysis revealed that the identified cDNA encodes a KDWK domain and contains sequences almost. . . mGMEB-1 bound specifically to GME oligonucleotides, either alone or as a heterodimer with rGMEB-2. Transient transfection experiments with TAT promoter **reporter genes** suggest a potential role for mGMEB-1 as a transcriptional regulator of the TAT promoter.

L8 ANSWER 12 OF 42 MEDLINE
ACCESSION NUMBER: 2001060564 MEDLINE
DOCUMENT NUMBER: 20519379 PubMed ID: 11064149
TITLE: Apparent coactivation due to interference of expression constructs with nuclear receptor expression.
AUTHOR: Hofman K; Swinnen J V; Claessens F; Verhoeven G; Heyns W
CORPORATE SOURCE: Laboratory for Experimental Medicine and Endocrinology, Faculty of Medicine, Catholic University of Leuven, B-3000, Leuven, Belgium.
SOURCE: MOLECULAR AND CELLULAR ENDOCRINOLOGY, (2000 Oct 25) 168 (1-2) 21-9.
Journal code: E69. ISSN: 0303-7207.
PUB. COUNTRY: Ireland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001222
AB . . . in COS-7 cells, a standard approach to demonstrate coactivation, was used to study the coactivation properties of NuRIP183, a new **nuclear receptor** interacting protein of 183 kDa, isolated by a yeast two-hybrid **screening**. Transfection with a NuRIP183 expression construct strongly increased the **ligand**-dependent response of **reporter** constructs for several **nuclear receptors** when compared to transfection with the empty expression vector. A more detailed study, however, revealed major changes in the expression level of the **nuclear receptors** in cotransfection experiments, indicating that the observed changes in receptor activity were not due to coactivation but to differences in. . . (FuGENE-6 and calcium phosphate) and different expression vectors (pSG5, pcDNA1.1 and pIRESneo). These data cast some doubt on coactivation of **nuclear receptors** based on similar cotransfection experiments without measurement of receptor concentration. Moreover, it is recommended to limit the amounts of (co)transfected. . .

L8 ANSWER 13 OF 42 MEDLINE
ACCESSION NUMBER: 2000092325 MEDLINE
DOCUMENT NUMBER: 20092325 PubMed ID: 10628744
TITLE: Protein inhibitor of activated STAT-1 (signal transducer and activator of transcription-1) is a nuclear receptor coregulator expressed in human testis.
AUTHOR: Tan J; Hall S H; Hamil K G; Grossman G; Petrusz P; Liao J; Shuai K; French F S
CORPORATE SOURCE: Department of Pediatrics, University of North Carolina School of Medicine, Chapel Hill 27599-7500, USA.
CONTRACT NUMBER: AI 43438 (NIAID)
R37 HD-04466 (NICHD)
T32 HD-07315 (NICHD)
+
SOURCE: MOLECULAR ENDOCRINOLOGY, (2000 Jan) 14 (1) 14-26.
Journal code: NGZ; 8801431. ISSN: 0888-8809.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF167160
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000204
Last Updated on STN: 20000204
Entered Medline: 20000124

AB An androgen receptor (AR) interacting protein was isolated from a HeLa cell cDNA library by two-hybrid **screening** in yeast using the AR DNA+**ligand** binding domains as bait. The protein has sequence identity with human protein inhibitor of activated signal transducer and activator of transcription (PIAS1) and human Gu RNA helicase II binding protein (GBP). Binding of PIAS1 to human AR DNA+**ligand** binding domains was androgen dependent in the yeast liquid beta-galactosidase assay. Activation of binding by dihydrotestosterone was greater than testosterone. . . matrix assays. In transient cotransfection assays using CV1 cells with full-length human AR and a mouse mammary tumor virus luciferase **reporter** vector, there was an androgen-dependent 3- to 5-fold greater increase in luciferase activity with PIAS1 over that obtained with an. . . Leydig cells. In addition, PIAS1 was expressed in spermatogenic cells. The results suggest that PIAS1 functions in testis as a **nuclear receptor** transcriptional coregulator and may have a role in AR initiation and maintenance of spermatogenesis.

L8 ANSWER 14 OF 42 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:641077 CAPLUS
DOCUMENT NUMBER: 131:267023
TITLE: Compositions and methods for detecting ligand-dependent nuclear receptor and coactivator interactions for drug screening
INVENTOR(S): Northrop, Jeffrey Paul; Hart, Charles Praray; Schatz, Peter Joseph
PATENT ASSIGNEE(S): Glaxo Group Ltd., UK
SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9950664	A1	19991007	WO 1999-US7168	19990401
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9935479	A1	19991018	AU 1999-35479	19990401
EP 1070254	A1	20010124	EP 1999-917331	19990401
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: US 1998-53611 A1 19980401
WO 1999-US7168 W 19990401

REFERENCE COUNT: 4
REFERENCE(S):
(1) Heery; Nature 1997, V387, P733 CAPLUS
(2) Le Douarin; Nucleic Acids Research 1995, V23(5), P876 CAPLUS
(3) Stahl; US 5470952 A 1995 CAPLUS
(4) Traish; Steroids 1996, V61(9), P549 CAPLUS

IT **Reporter gene**

RL: ARG (Analytical reagent use); BPN (Biosynthetic preparation); BPR (Biological process); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(in **nuclear receptor** signal transduction system; compns. and methods for detecting **ligand**-dependent **nuclear receptor** and coactivator interactions for drug **screening**)

IT 9014-00-0P, Luciferase
RL: ARG (Analytical reagent use); BPN (Biosynthetic preparation); BPR (Biological process); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(**reporter**; compns. and methods for detecting **ligand**-dependent **nuclear receptor** and coactivator interactions for drug **screening**)

L8 ANSWER 15 OF 42 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:626216 CAPLUS
DOCUMENT NUMBER: 131:267021
TITLE: Orphan nuclear receptor binding CYP promoter for drug screening
INVENTOR(S): Kliewer, Steven Anthony; Willson, Timothy Mark
PATENT ASSIGNEE(S): Glaxo Group Limited, UK
SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9948915	A1	19990930	WO 1999-US6737	19990326
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9932116	A1	19991018	AU 1999-32116	19990326
EP 1066320	A1	20010110	EP 1999-914221	19990326
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: US 1998-79593 A2 19980327
WO 1999-US6737 W 19990326
OTHER SOURCE(S): MARPAT 131:267021
REFERENCE COUNT: 1
REFERENCE(S): (1) Bertilsson; Proc Natl Acad Sci USA 1998, V95, P12208 CAPLUS

IT **Reporter gene**
RL: BPR (Biological process); PEP (Physical, engineering or chemical process); BIOL (Biological study); PROC (Process)
(orphan **nuclear receptor** binding CYP promoter for drug **screening**)

L8 ANSWER 16 OF 42 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:96372 CAPLUS
DOCUMENT NUMBER: 130:163951
TITLE: Cloning of cDNA for ligand-converting enzymes from mice and human, and methods of screening nuclear receptors-binding ligands or transcription factors
INVENTOR(S): Kato, Shigeaki; Takeyama, Ken-ichi; Kitanaka, Sachiko
PATENT ASSIGNEE(S): Chugai Seiyaku Kabushiki Kaisha, Japan
SOURCE: PCT Int. Appl., 66 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9905292	A1	19990204	WO 1998-JP3280	19980722
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9883564	A1	19990216	AU 1998-83564	19980722
JP 11127871	A2	19990518	JP 1998-206786	19980722
EP 1024193	A1	20000802	EP 1998-933895	19980722
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: JP 1997-212624 A 19970722
WO 1998-JP3280 W 19980722

REFERENCE COUNT: 14
REFERENCE(S):
(1) Cali, J; J Biol Chem 1991, V266(12), P7774 CAPLUS
(2) Cali, J; J Biol Chem 1991, V266(12), P7779 CAPLUS
(3) Fu, G; DNA Cell Biol 1997, V16(12), P1499 CAPLUS
(4) Fu, G; Mol Endocrinol 1997, V11(13), P1961 CAPLUS
(5) Guo, Y; Proc Natl Acad Sci USA 1993, V90(18), P8668 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Described are transgenic cells to be used for **screening** enzyme proteins that convert **ligand** precursors into **ligands**, which bind to a **nuclear receptor** and induces the transcription of a **reporter gene** downstream and (2) a method of isolating the protein-encoding **gene**. The cells are transformed with a recombinant DNA encoding the DNA-binding domain of yeast GAL4, the **ligand**-binding domain of vitamin D receptor, and a **reporter gene** such as lacZ. The **ligand** -receptor-induced transcription system can be used for **screening ligands** and the enzymes capable of converting an inactive transcription-regulating factor into an active one. Cloning of cDNAs encoding 507-amino-acid CYP1AD, which converts inactive 25(OH)D3 into active 1.alpha.,25(OH)2D3, from a mouse (Mus musculus) kidney cDNA library and 508-amino-acid vitamin D 1.alpha.-hydroxylase from a human kidney cDNA library was shown.

IT lacZ **gene** (microbial)
RL: BPR (Biological process); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(**reporter**; cloning of cDNA for **ligand**-converting enzymes from mice and human, and methods of **screening** **nuclear receptors**-binding **ligands** or transcription factors)

L8 ANSWER 17 OF 42 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:34993 CAPLUS
DOCUMENT NUMBER: 130:106061
TITLE: Novel **reporter** plasmid vectors for **screening ligands** that bind to **nuclear receptors** and use for **screening** drugs for cancer or autoimmune diseases
INVENTOR(S): Hagiya, Hiroshi; Minami, Masashi; Tajima, Hisao

PATENT ASSIGNEE(S): Ono Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9900491	A1	19990107	WO 1998-JP2785	19980623
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9880386	A1	19990119	AU 1998-80386	19980623
EP 1016714	A1	20000705	EP 1998-928625	19980623
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: JP 1997-171440 A 19970627
WO 1998-JP2785 W 19980623

REFERENCE COUNT: 7
REFERENCE(S):
(1) Kawaguchi, Y; Cancer Letters 1997, V116, P53 CAPLUS
(2) Ono Pharmaceutical Co Ltd; JP 07316200 A 1995 CAPLUS
(3) Salk Inst Biological Studies; WO 9640128 A 1996 CAPLUS
(4) The Salk Institute For Biological Studies; EP 737314 A CAPLUS
(5) The Salk Institute For Biological Studies; AU 9514366 A CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Novel **reporter** plasmid vectors for **screening** **ligands** that bind to **nuclear receptors** and use for **screening** drugs for cancer or autoimmune diseases

AB Described are a plasmid vector encoding a **reporter**; a transgenic cell transformed by the plasmid and a plasmid expressing an effector protein-encoding **gene**; and a method of using the transgenic cell for **screening ligands** that bind the cognate **nuclear receptors**. Prepn. of a **reporter** plasmid carrying the Gal4-responsive element, the TK promoter of herpes simplex virus, and the mouse Fas-encoding sequence; prepn. of an effector-expressing plasmid encoding a fusion protein of the DNA-binding domain of Gal4 and the **ligand**-binding domain of human peroxisome proliferator-activated receptor (PPAR) .gamma., .gamma. or .delta.; transformation of mouse fibroblasts L929 with **reporter** plasmid and the effector-expressing plasmid; and cultivation of the transgenic cells for selecting **ligand**-responsive clones using the PPAR.gamma. **ligands** CS-045 and BRL-49653 were demonstrated. The system is useful for **screening ligands** cognate to the **nuclear receptors** for use as therapeutic agents for cancer or autoimmune diseases, which **ligands** induce apoptosis, . Claimed are the **reporter** plasmids contg. the sequence encoding 136-305-Fas antigen of mice or 145-319-Fas antigen of human, with(out) the signal sequence; the effector plasmids contg. 167-468-PPAR-.alpha. of human or mice, 139-441-PPAR .delta. of human, 138-440-PPAR .delta. of mice, 176-478-PPAR .gamma.1 of human, 174-475-PPAR .gamma.1 of mice, 204-506-PPAR .gamma.2 of human, 204-505-PPAR .gamma.2 of mice, other defined **nuclear receptors**; and methods of using the transgenic cells for **screening** therapeutic agents for cancer or

autoimmune diseases.

IT Apoptosis
(Fas antigen-induced; novel plasmid vectors contg. a **reporter gene** for **screening ligands** that bind to **nuclear receptors** and use for **screening** drugs for cancer or autoimmune diseases)

IT Antitumor agents
Autoimmune diseases
Drug **screening**
Plasmid vectors
(novel plasmid vectors contg. a **reporter gene** for **screening ligands** that bind to **nuclear receptors** and use for **screening** drugs for cancer or autoimmune diseases)

IT Fas antigen
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(novel plasmid vectors contg. a **reporter gene** for **screening ligands** that bind to **nuclear receptors** and use for **screening** drugs for cancer or autoimmune diseases)

IT **Ligands**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(novel plasmid vectors contg. a **reporter gene** for **screening ligands** that bind to **nuclear receptors** and use for **screening** drugs for cancer or autoimmune diseases)

IT GAL4 transcription factor
Nuclear receptors
Retinoid receptors
Thyroid hormone receptors
Vitamin D receptors
RL: BPR (Biological process); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(novel plasmid vectors contg. a **reporter gene** for **screening ligands** that bind to **nuclear receptors** and use for **screening** drugs for cancer or autoimmune diseases)

IT Peroxisome proliferator-activated receptors
RL: BPR (Biological process); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(.alpha.; novel plasmid vectors contg. a **reporter gene** for **screening ligands** that bind to **nuclear receptors** and use for **screening** drugs for cancer or autoimmune diseases)

IT Peroxisome proliferator-activated receptors
RL: BPR (Biological process); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(.gamma.; novel plasmid vectors contg. a **reporter gene** for **screening ligands** that bind to **nuclear receptors** and use for **screening** drugs for cancer or autoimmune diseases)

IT Peroxisome proliferator-activated receptors
RL: BPR (Biological process); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(.delta.; novel plasmid vectors contg. a **reporter gene** for **screening ligands** that bind to **nuclear receptors** and use for **screening** drugs for cancer or autoimmune diseases)

L8 ANSWER 18 OF 42 USPATFULL

ACCESSION NUMBER: 1999:170596 USPATFULL
TITLE: Synthesis and use of retinoid compounds having negative
hormone and/or antagonist activities
INVENTOR(S): Klein, Elliott S., Marina del Rey, CA, United States
Johnson, Alan T., Rancho Santa Margarita, CA, United States
Standeven, Andrew M., Corona del Mar, CA, United States
Beard, Richard L., Newport Beach, CA, United States
Gillett, Samuel J., Albany, CA, United States
Duong, Tien T., Irvine, CA, United States
Nagpal, Sunil, Lake Forest, CA, United States
Vuligonda, Vidyasagar, Irvine, CA, United States
Teng, Min, Aliso Viejo, CA, United States
Chandraratna, Roshantha A., Mission Viejo, CA, United States
PATENT ASSIGNEE(S): Allergan Sales, Inc., Irvine, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6008204		19991228
APPLICATION INFO.:	US 1998-222983		19981230 (9)

RELATED APPLN. INFO.: Division of Ser. No. US 1997-871093, filed on 9 Jun 1997 which is a division of Ser. No. US 1996-613863, filed on 11 Mar 1996, now patented, Pat. No. US 5776699

	NUMBER	DATE
PRIORITY INFORMATION:	US 1995-19015	19950901 (60)
	US 1995-64853	19951013 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Shah, Mukund J.
ASSISTANT EXAMINER: Rao, Deepak R.
LEGAL REPRESENTATIVE: Szekeres, Gabor L., Baran, Robert J., Voet, Martin A.
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 30 Drawing Figure(s); 15 Drawing Page(s)
LINE COUNT: 6383
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD Our method of RAR negative hormone **screening** based on the use of CV- 1 cells co-transfected with the ERE-tk-Luc luciferase **reporter** plasmid and the ER-RXR-.alpha. and RAR-.gamma.-VP-16 receptor expression plasmids can be adapted generally such that the RAR-.gamma. moiety of the. . . to that of peroxisome proliferator-activated receptors (PPAR), vitamin D receptor (VDR), thyroid hormone receptor (T3R) or any other steroid superfamily **nuclear receptor** capable of heterodimerizing with RXR. CV-1 cells co-transfected with such plasmids would express high basal levels of luciferase activity. **Ligands** capable of binding the **ligand** binding domain of the receptor substituted for the RAR-.gamma. moiety can be easily **screened** for negative hormone activity by measuring their ability to repress luciferase activity.

DETD For steroid superfamily **nuclear receptors** that do not heterodimerize with RXR (e.g., glucocorticoid and estrogen receptors) the same end result can be achieved using GR-VP-16 or ER-VP-16 receptors and a luciferase **reporter** plasmid consisting of the appropriate glucocorticoid or estrogen response element fused to a heterologous promoter element and luciferase or other **reporter gene**. An essential feature of a generalized negative hormone **screening** assay is the inclusion of at least the **ligand** binding domain of the particular **nuclear**

receptor for which inverse agonists are to be **screened** and a method for localizing the **nuclear receptor** **ligand** binding domain to the promoter of a **reporter** **gene**. This could be achieved using the receptors's natural DNA binding site, or alternatively by construction of a chimeric receptor having a heterologous DNA binding domain and corresponding use of a **reporter gene** which is under control of a DNA regulatory element which is recognized by the heterologous DNA binding domain. In a preferred embodiment, the plasmid expressing the **nuclear receptor** for which inverse agonists are to be **screened** would express this **nuclear receptor** as a fusion protein containing a constitutive activation domain, such as the HSV VP-16 activation domain, in order to provide allow high basal activity. This high basal activity would effectively increase assay sensitivity, thereby allowing analysis of **nuclear** **receptor ligands** which repress basal transcriptional activity in the absence of added **nuclear receptor** agonist.

L8 ANSWER 19 OF 42 USPATFULL

ACCESSION NUMBER:	1999:155937 USPATFULL
TITLE:	Activators of the nuclear orphan receptor peroxisome proliferator-activated receptor gamma
INVENTOR(S):	Kliewer, Steven Anthony, Cary, NC, United States Lehmann, Jurgen M., Chapel Hill, NC, United States Willson, Timothy M., Durham, NC, United States
PATENT ASSIGNEE(S):	Glaxo Wellcome Inc., Research Triangle Park, NC, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5994554		19991130
APPLICATION INFO.:	US 1998-207936		19981209 (9)

RELATED APPLN. INFO.: Division of Ser. No. US 1998-28988, filed on 25 Feb 1998, now patented, Pat. No. US 5902726 which is a continuation of Ser. No. US 1997-804310, filed on 21 Feb 1997, now abandoned which is a continuation of Ser. No. US 1995-386394, filed on 10 Feb 1995, now abandoned which is a continuation-in-part of Ser. No. US 1994-363482, filed on 23 Dec 1994, now abandoned

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Shah, Mukund J.
ASSISTANT EXAMINER:	Sripada, Pavanaram K.
LEGAL REPRESENTATIVE:	Brink, Robert H.
NUMBER OF CLAIMS:	6
EXEMPLARY CLAIM:	1
LINE COUNT:	686

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD A transient cotransfection assay was used to **screen** for activators of PPAR.gamma.. As mammalian cell lines contain endogenous **nuclear receptors** that can complicate interpretation of the results, we used an established chimera system in which the **ligand**-binding domain of the murine PPAR.gamma. was fused to the DNA binding domain of the yeast transcription factor GAL4. The GAL4-PPAR.gamma. chimera was cotransfected into CV-1 cells with a **reporter** construct containing five copies of the GAL4 binding site upstream of the thymidine kinase promoter driving secreted placental alkaline phosphatase (SPAP) as **reporter**. Data is seen in the table below.

L8 ANSWER 20 OF 42 USPATFULL

ACCESSION NUMBER: 1999:117525 USPATFULL
TITLE: Synthesis and use of retinoid compounds having negative hormone and/or antagonist activities
INVENTOR(S): Klein, Elliott S., Marina del Rey, CA, United States
Johnson, Alan T., Rancho Santa Margarita, CA, United States
Standeven, Andrew M., Ventura, CA, United States
Beard, Richard L., Newport Beach, CA, United States
Gillett, Samuel J., Albany, CA, United States
Duong, Tien T., Irvine, CA, United States
Nagpal, Sunil, Lake Forest, CA, United States
Vuligonda, Vidyasagar, Irvine, CA, United States
Teng, Min, San Diego, CA, United States
Chandraratna, Roshantha A., Mission Viejo, CA, United States
PATENT ASSIGNEE(S): Allergan Sales, Inc., Irvine, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5958954		19990928
APPLICATION INFO.:	US 1997-998319		19971224 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1997-871093, filed on 9 Jun 1997 which is a division of Ser. No. US 1996-613863, filed on 11 Mar 1996, now patented, Pat. No. US 5776699

	NUMBER	DATE
PRIORITY INFORMATION:	US 1995-19015	19950901 (60)
	US 1995-64853	19951013 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Shah, Mukund J.
ASSISTANT EXAMINER: Rao, Deepak R.
LEGAL REPRESENTATIVE: Szekeres, Gabor L., Baran, Robert J., Voet, Martin A.
NUMBER OF CLAIMS: 46
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 31 Drawing Figure(s); 20 Drawing Page(s)
LINE COUNT: 8337
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD Our method of RAR negative hormone **screening** based on the use of CV-1 cells co-transfected with the ERE-tk-Luc luciferase **reporter** plasmid and the ER-RXR-A and RAR-.gamma.-VP-16 receptor expression plasmids can be adapted generally such that the RAR-.gamma. moiety of the. . . to that of peroxisome proliferator-activated receptors (PPAR), vitamin D receptor (VDR), thyroid hormone receptor (T3R) or any other steroid superfamily **nuclear receptor** capable of heterodimerizing with RXR. CV-1 cells co-transfected with such plasmids would express high basal levels of luciferase activity. **Ligands** capable of binding the **ligand** binding domain of the receptor substituted for the RAR-.gamma. moiety can be easily **screened** for negative hormone activity by measuring their ability to repress luciferase activity.

DETD For steroid superfamily **nuclear receptors** that do not heterodimerize with RXR (e.g., glucocorticoid and estrogen receptors) the same end result can be achieved using GR-VP-16 or ER-VP-16 receptors and a luciferase **reporter** plasmid consisting of the appropriate glucocorticoid or estrogen response element fused to a heterologous promoter element and luciferase or other **reporter gene**. An essential feature of a generalized negative hormone **screening** assay is the inclusion of at least the **ligand** binding domain of the particular **nuclear receptor** for which inverse agonists are to be **screened**

and a method for localizing the **nuclear receptor** **ligand** binding domain to the promoter of a **reporter** **gene**. This could be achieved using the receptors's natural DNA binding site, or alternatively by construction of a chimeric receptor having a heterologous DNA binding domain and corresponding use of a **reporter gene** which is under control of a DNA regulatory element which is recognized by the heterologous DNA binding domain. In a preferred embodiment, the plasmid expressing the **nuclear receptor** for which inverse agonists are to be **screened** would express this **nuclear receptor** as a fusion protein containing a constitutive activation domain, such as the HSV VP-16 activation domain, in order to provide allow high basal activity. This high basal activity would effectively increase assay sensitivity, thereby allowing analysis of **nuclear** **receptor** **ligands** which repress basal transcriptional activity in the absence of added **nuclear receptor** agonist.

L8 ANSWER 21 OF 42 USPATFULL

ACCESSION NUMBER:	1999:117275 USPATFULL
TITLE:	Use of modified tethers in screening compound libraries
INVENTOR(S):	Dower, William J., Menlo Park, CA, United States Heinkel, Gregory L., San Jose, CA, United States Mattheakis, Larry, Cupertino, CA, United States Schatz, Peter J., Mountain View, CA, United States
PATENT ASSIGNEE(S):	Glaxo Group Limited, Greenford, United Kingdom (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5958703		19990928	
APPLICATION INFO.:	US 1996-758307		19961203	(8)
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Achutamurthy, Ponnathapura			
ASSISTANT EXAMINER:	Ricigliano, Joseph W			
LEGAL REPRESENTATIVE:	Liebeschuetz, Joe, Stevens, Lauren L.			
NUMBER OF CLAIMS:	44			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	10 Drawing Figure(s); 9 Drawing Page(s)			
LINE COUNT:	1915			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD The regulatory sequences depend on the target receptor. For example, to **screen** for activators of 7TM receptors, the recombinase is placed under the transcriptional control of a promoter which responds to 7TM. . . promoter composed of repeating cyclic AMP response elements, or the Fus1 promoter if the 7TM receptor is expressed in yeast **reporter** cells. As a further example, to **screen** for activation of a T-cell receptor, the recombinase can be linked to an NFAT promoter. In a further variation, the. . . target receptor, such that the recombinase is inactive in the fusion protein unless the fusion protein is bound to a **ligand**, which causes steric changes that activate the recombinase. Activation of recombinases fused to **ligand** binding domains of **nuclear receptors** on **ligand** binding has been reported. See Logie & Stewart, Proc. Natl. Acad. Sci. USA 92, 5940-5944 (1995); Metzger et al., Proc. Natl. Acad. Sci. USA 92, 6991-6995 (1995). Suitable **nuclear** **receptors** include estrogen, glucocorticoid and androgen receptors.

L8 ANSWER 22 OF 42 USPATFULL

ACCESSION NUMBER: 1999:110335 USPATFULL

TITLE: Synthesis and use of retinoid compounds having negative hormone and/or antagonist activities

INVENTOR(S): Klein, Elliot S., Marina del Rey, CA, United States
Johnson, Alan T., Rancho Santa Margarita, CA, United States
Standeven, Andrew M., Corona del Mar, CA, United States
Beard, Richard L., Newport Beach, CA, United States
Gillett, Samuel J., Albany, CA, United States
Duong, Tien T., Irvine, CA, United States
Nagpal, Sunil, Lake Forest, CA, United States
Vuligonda, Vidyasagar, Irvine, CA, United States
Teng, Min, Aliso Viejo, CA, United States
Chandraratna, Roshantha A., Mission Viejo, CA, United States

PATENT ASSIGNEE(S): Allergan Sales, Inc., Irvine, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5952345		19990914
APPLICATION INFO.:	US 1997-871093		19970609 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1996-613863, filed on 11 Mar 1996, now patented, Pat. No. US 5776699

	NUMBER	DATE
PRIORITY INFORMATION:	US 1995-19015	19950901 (60)
	US 1995-64853	19951013 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Raymond, Richard L.
ASSISTANT EXAMINER: Rao, Deepak R.
LEGAL REPRESENTATIVE: Szekeres, Gabor L., Baran, Robert J., Voet, Martin A.
NUMBER OF CLAIMS: 31
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 20 Drawing Figure(s); 15 Drawing Page(s)
LINE COUNT: 6600
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD Our method of RAR negative hormone **screening** based on the use of CV-1 cells co-transfected with the ERE-tk-Luc luciferase **reporter** plasmid and the ER-RXR-.alpha. and RAR-.gamma.-VP-16 receptor expression plasmids can be adapted generally such that the RAR-.gamma. moiety of the. . . to that of peroxisome proliferator-activated receptors (PPAR), vitamin D receptor (VDR), thyroid hormone receptor (T3R) or any other steroid superfamily **nuclear receptor** capable of heterodimerizing with RXR. CV-1 cells co-transfected with such plasmids would express high basal levels of luciferase activity. **Ligands** capable of binding the **ligand** binding domain of the receptor substituted for the RAR-.gamma. moiety can be easily **screened** for negative hormone activity by measuring their ability to repress luciferase activity.

DETD For steroid superfamily **nuclear receptors** that do not heterodimerize with RXR (e.g., glucocorticoid and estrogen receptors) the same end result can be achieved using GR-VP-16 or ER-VP-16 receptors and a luciferase **reporter** plasmid consisting of the appropriate glucocorticoid or estrogen response element fused to a heterologous promoter element and luciferase or other **reporter gene**. An essential feature of a generalized negative hormone **screening** assay is the inclusion of at least the **ligand** binding domain of the particular **nuclear receptor** for which inverse agonists are to be **screened**

and a method for localizing the **nuclear receptor** **ligand** binding domain to the promoter of a **reporter** **gene**. This could be achieved using the receptors's natural DNA binding site, or alternatively by construction of a chimeric receptor having a heterologous DNA binding domain and corresponding use of a **reporter gene** which is under control of a DNA regulatory element which is recognized by the heterologous DNA binding domain. In a preferred embodiment, the plasmid expressing the **nuclear receptor** for which inverse agonists are to be **screened** would express this **nuclear receptor** as a fusion protein containing a constitutive activation domain, such as the HSV VP-16 activation domain, in order to provide allow high basal activity. This high basal activity would effectively increase assay sensitivity, thereby allowing analysis of **nuclear** **receptor ligands** which repress basal transcriptional activity in the absence of added **nuclear receptor** agonist.

L8 ANSWER 23 OF 42 USPATFULL
ACCESSION NUMBER: 1999:56399 USPATFULL
TITLE: Activators of the nuclear orphan receptor peroxisome proliferator-activated receptor gamma
INVENTOR(S): Kliewer, Steven Anthony, Cary, NC, United States
Lehmann, Jurgen M., Chapel Hill, NC, United States
Willson, Timothy M., Durham, NC, United States
PATENT ASSIGNEE(S): Glaxo Wellcome Inc., Research Triangle Park, NC, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5902726		19990511
APPLICATION INFO.:	US 1998-28988		19980225 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1997-804310, filed on 21 Feb 1997, now abandoned which is a continuation of Ser. No. US 1995-386394, filed on 10 Feb 1995, now abandoned which is a continuation-in-part of Ser. No. US 1994-363482, filed on 23 Dec 1994, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Gupta, Yogendra N.
LEGAL REPRESENTATIVE: Brink, Robert H.
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
LINE COUNT: 791
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD A transient cotransfection assay was used to **screen** for activators of PPAR.gamma.. As mammalian cell lines contain endogenous **nuclear receptors** that can complicate interpretation of the results, we used an established chimera system in which the **ligand**-binding domain of the murine PPAR.gamma. was fused to the DNA binding domain of the yeast transcription factor GAL4. The GAL4-PPAR.gamma. chimera was cotransfected into CV-1 cells with a **reporter** construct containing five copies of the GAL4 binding site upstream of the thymidine kinase promoter driving secreted placental alkaline phosphatase (SPAP) as **reporter**. Data is seen in the table below.

L8 ANSWER 24 OF 42 USPATFULL
ACCESSION NUMBER: 1999:27666 USPATFULL
TITLE: Synthesis and use of retinoid compounds having negative hormone and/or antagonist activities

INVENTOR(S): Klein, Elliott S., Marina del Rey, CA, United States
Johnson, Alan T., Rancho Santa Margarita, CA, United States
Standeven, Andrew M., Corona del Mar, CA, United States
Beard, Richard L., Newport Beach, CA, United States
Gillett, Samuel J., Oakland, CA, United States
Duong, Tien T., Irvine, CA, United States
Nagpal, Sunil, Irvine, CA, United States
Vuligonda, Vidyasagar, Irvine, CA, United States
Teng, Min, Aliso Viejo, CA, United States
Chandraratna, Roshantha A., Mission Viejo, CA, United States
PATENT ASSIGNEE(S): Allergan Sales, Inc., Irvine, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5877207		19990302
APPLICATION INFO.:	US 1997-880823		19970624 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1996-613863, filed on 11 Mar 1996, now patented, Pat. No. US 5776699

	NUMBER	DATE
PRIORITY INFORMATION:	US 1995-19015	19950901 (60)
	US 1995-64853	19951013 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Richter, Johann
ASSISTANT EXAMINER: Solola, Taofiq A.
LEGAL REPRESENTATIVE: Szekeres, Garbor L., Baran, Robert J., Voet, Martin S.
NUMBER OF CLAIMS: 34
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 30 Drawing Figure(s); 15 Drawing Page(s)
LINE COUNT: 6732
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD Our method of RAR negative hormone **screening** based on the use of CV-1 cells co-transfected with the ERE-tk-Luc luciferase **reporter** plasmid and the ER-RXR-.alpha. and RAR-.gamma.-VP-16 receptor expression plasmids can be adapted generally such that the RAR-.gamma. moiety of the. . . to that of peroxisome proliferator-activated receptors (PPAR), vitamin D receptor (VDR), thyroid hormone receptor (T3R) or any other steroid superfamily **nuclear receptor** capable of heterodimerizing with RXR. CV-1 cells co-transfected with such plasmids would express high basal levels of luciferase activity. **Ligands** capable of binding the **ligand** binding domain of the receptor substituted for the RAR-.gamma. moiety can be easily **screened** for negative hormone activity by measuring their ability to repress luciferase activity.

DETD For steroid superfamily **nuclear receptors** that do not heterodimerize with RXR (e.g., glucocorticoid and estrogen receptors) the same end result can be achieved using GR-VP-16 or ER-VP-16 receptors and a luciferase **reporter** plasmid consisting of the appropriate glucocorticoid or estrogen response element fused to a heterologous promoter element and luciferase or other **reporter gene**. An essential feature of a generalized negative hormone **screening** assay is the inclusion of at least the **ligand** binding domain of the particular **nuclear receptor** for which inverse agonists are to be **screened** and a method for localizing the **nuclear receptor ligand** binding domain to the promoter of a **reporter gene**. This could be achieved using the receptors's natural DNA binding site, or alternatively by construction of a chimeric receptor having a heterologous DNA binding domain and corresponding use of a

reporter gene which is under control of a DNA regulatory element which is recognized by the heterologous DNA binding domain. In a preferred embodiment, the plasmid expressing the **nuclear receptor** for which inverse agonists are to be **screened** would express this **nuclear receptor** as a fusion protein containing a constitutive activation domain, such as the HSV VP-16 activation domain, in order to provide allow high basal activity. This high basal activity would effectively increase assay sensitivity, thereby allowing analysis of **nuclear receptor ligands** which repress basal transcriptional activity in the absence of added **nuclear receptor** agonist.

L8 ANSWER 25 OF 42 MEDLINE
ACCESSION NUMBER: 1999357798 MEDLINE
DOCUMENT NUMBER: 99357798 PubMed ID: 10428842
TITLE: Hormone-independent transcriptional activation and coactivator binding by novel orphan nuclear receptor ERR3.
AUTHOR: Hong H; Yang L; Stallcup M R
CORPORATE SOURCE: Department of Pathology, University of Southern California, Los Angeles, California 90033, USA.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Aug 6) 274 (32) 22618-26.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF117254; GENBANK-AF117255
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19990913
Last Updated on STN: 19990913
Entered Medline: 19990902
AB Orphan **nuclear receptors** share sequence homology with members of the **nuclear receptor** superfamily, but **ligands** are unknown or unnecessary. A novel orphan receptor, estrogen receptor-related protein 3 (ERR3), was identified by yeast two-hybrid **screening**, using the transcriptional coactivator glucocorticoid receptor interacting protein 1 (GRIP1) as bait. The putative full-length mouse ERR3 contains 458 amino. . . has 68% amino acid identity with that of estrogen receptor. ERR3 bound specifically to an estrogen response element and activated **reporter genes** controlled by estrogen response elements, both in yeast and in mammalian cells, in the absence of any added **ligand**. A conserved AF-2 activation domain located in the hormone-binding domain of ERR3 was primarily responsible for transcriptional activation. The ERR3 AF-2 domain bound GRIP1 in a **ligand**-independent manner both in vitro and in vivo, through the LXXLL motifs of GRIP1, and GRIP1 functioned as a transcriptional coactivator. . .

L8 ANSWER 26 OF 42 MEDLINE
ACCESSION NUMBER: 2000079622 MEDLINE
DOCUMENT NUMBER: 20079622 PubMed ID: 10611353
TITLE: Retina-specific nuclear receptor: A potential regulator of cellular retinaldehyde-binding protein expressed in retinal pigment epithelium and Muller glial cells.
AUTHOR: Chen F; Figueroa D J; Marmorstein A D; Zhang Q; Petrukhin K; Caskey C T; Austin C P
CORPORATE SOURCE: Department of Human Genetics, Merck Research Laboratories, West Point, PA 19486, USA.. fang_chen@merck.com
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE

UNITED STATES OF AMERICA, (1999 Dec 21) 96 (26) 15149-54.

Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF148128; GENBANK-AF148129
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000204
Last Updated on STN: 20000204
Entered Medline: 20000127

AB In an effort to identify **nuclear receptors** important in retinal disease, we **screened** a retina cDNA library for **nuclear receptors**. Here we describe the identification of a retina-specific **nuclear receptor** (RNR) from both human and mouse. Human RNR is a splice variant of the recently published photoreceptor cell-specific **nuclear receptor** [Kobayashi, M., Takezawa, S., Hara, K., Yu, R. T., Umesono, Y., Agata, K., Taniwaki, M., Yasuda, K. & Umesono, K.. . . demonstrates that RNR is expressed in the retinal pigment epithelium and in Muller glial cells. By using the Gal4 chimeric receptor/**reporter** cotransfection system, the **ligand** binding domain of RNR was found to repress transcriptional activity in the absence of exogenous **ligand**. Gel mobility shift assays revealed that RNR can interact with the promoter of the cellular retinaldehyde binding protein **gene** in the presence of retinoic acid receptor (RAR) and/or retinoid X receptor (RXR). These data raise the possibility that RNR. . .

L8 ANSWER 27 OF 42 MEDLINE
ACCESSION NUMBER: 2000027537 MEDLINE
DOCUMENT NUMBER: 20027537 PubMed ID: 10557310
TITLE: Feedback-inducible nuclear-receptor-driven reporter gene expression in transgenic mice.
AUTHOR: Mata De Urquiza A; Solomin L; Perlmann T
CORPORATE SOURCE: Ludwig Institute for Cancer Research, Karolinska Institute, S-171 77 Stockholm, Sweden.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Nov 9) 96 (23) 13270-5.
Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991213

AB Understanding **nuclear receptor** signaling in vivo would be facilitated by an efficient methodology to determine where a **nuclear receptor** is active. Herein, we present a feedback-inducible expression system in transgenic mice to detect activated **nuclear receptor** effector proteins by using an inducible **reporter gene**. With this approach, **reporter gene** induction is not limited to a particular tissue, and, thus, this approach provides the opportunity for whole-animal **screens**. Furthermore, the effector and **reporter genes** are combined to generate a single strain of transgenic mice, which enables direct and rapid analysis of the offspring. The system was applied to localize sites where the retinoic acid receptor **ligand** -binding domain is activated in vivo. The results identify previously discovered sources of retinoids in the embryo and indicate the existence of previously undiscovered regions of retinoic acid receptor signaling in

vivo. Notably, the feedback-inducible **nuclear-receptor**-driven assay, combined with an independent in vitro assay, provides evidence for a site of retinoid synthesis in the isthmic mesenchyme. These data illustrate the potential of feedback-inducible **nuclear-receptor**-driven analyses for assessing in vivo activation patterns of **nuclear receptors** and for analyzing pharmacological properties of natural and synthetic **ligands** of potential therapeutic value.

L8 ANSWER 28 OF 42 MEDLINE
ACCESSION NUMBER: 1999421242 MEDLINE
DOCUMENT NUMBER: 99421242 PubMed ID: 10493499
TITLE: Two organochlorine pesticides, toxaphene and chlordane, are antagonists for estrogen-related receptor alpha-1 orphan receptor.
AUTHOR: Yang C; Chen S
CORPORATE SOURCE: Division of Immunology, Beckman Research Institute of the City of Hope, Duarte, California 91010, USA.
CONTRACT NUMBER: CA 65767 (NCI)
CA44735 (NCI)
ES08258 (NIEHS)
SOURCE: CANCER RESEARCH, (1999 Sep 15) 59 (18) 4519-24.
Journal code: CNF; 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991026
Last Updated on STN: 19991026
Entered Medline: 19991008

AB Estrogen-related receptor (ERR) alpha-1 shares a high amino acid sequence homology with estrogen receptor alpha. Although estrogens are not **ligands** of ERR alpha-1, our recent results suggest that toxaphene and chlordane, two organochlorine pesticides with estrogen-like activity, behave as antagonists for this orphan **nuclear receptor**. The two compounds increased ERR alpha-1-mediated expression of the **reporter** enzyme beta-galactosidase in a yeast-based assay. The **screen** was developed by expressing the hERR alpha-1-yeast Gal 4 activation domain fusion protein in yeast cells carrying the beta-galactosidase **reporter** plasmid, which contains an ERR alpha-1-binding element. In transfection experiments using mammalian cell lines, such as the SK-BR-3 breast cancer cell line, the compounds were found to have an antagonist activity against ERR alpha-1-mediated expression of the **reporter** chloramphenicol acetyltransferase. In contrast to the findings with ERR alpha-1, the two compounds were found to slightly induce the estrogen receptor a-mediated expression of chloramphenicol acetyltransferase in SK-BR-3 cells. In a **ligand**-independent manner, the ERR alpha-1 activity in SK-BR-3 cells was induced 3-fold by cotransfection with the GRIP1 coactivator expression plasmid. Toxaphene. . .

L8 ANSWER 29 OF 42 MEDLINE
ACCESSION NUMBER: 2000045093 MEDLINE
DOCUMENT NUMBER: 20045093 PubMed ID: 10574783
TITLE: Expression of cre recombinase as a reporter of signal transduction in mammalian cells.
AUTHOR: Mattheakis L C; Olivan S E; Dias J M; Northrop J P
CORPORATE SOURCE: Affymax Research Institute, Palo Alto, CA 94304, USA.. larry_mattheakis@affymax.com
SOURCE: CHEMISTRY AND BIOLOGY, (1999 Nov) 6 (11) 835-44.
Journal code: CNA; 9500160. ISSN: 1074-5521.

PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000209
Last Updated on STN: 20000209
Entered Medline: 20000131

AB BACKGROUND: Cell-based **reporter** assays, which rely on a **reporter gene** under the control of a regulated promoter, are widely used to **screen** chemical libraries for novel receptor **ligands**. Here, we describe a **reporter** system that is based on **ligand**-induced DNA recombination to express the **reporter gene**. This system converts a transient activation of a signal transduction pathway into an amplified, constitutive and heritable expression of the **reporter gene**. RESULTS: We constructed **gene** fusions of Cre recombinase and mammalian promoters regulated by calcium, **nuclear receptors** or cyclic AMP. **Reporter** systems, comprising a Cre **gene** fusion and a loxP/**reporter gene**, were used to study the kinetics and dose responses to compounds that activate or inhibit the corresponding signal transduction pathway. We compared these **reporters** with conventional **reporter** systems in which the **reporter gene** is under the direct control of the responsive promoter. **Reporter gene** expression of the Cre **reporters** was greater than that of conventional **reporters** and could be measured more than a week after adding the stimulus. For all pathways studied here, the dose responses of the Cre **reporters** are nearly identical to those of conventional **reporter** systems. CONCLUSIONS: We have shown that Cre recombinase can be regulated by a variety of signal transduction pathways. It should therefore be possible to use receptor **ligands** to induce phenotypic conversion of mammalian cells for use in a variety of applications. One such application is high-throughput **screening**, and we developed loxP/luciferase **reporter genes** that provide an amplified and sustained luminescent response.

L8 ANSWER 30 OF 42 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:260882 CAPLUS
DOCUMENT NUMBER: 133:203715
TITLE: Transcriptional regulation of the cholesterol 7.alpha.-hydroxylase gene (CYP7A) by nuclear hormone receptors bound to the bile acid response elements (BARE)
AUTHOR(S): Chiang, J. Y. L.; Stroup, D.; Crestani, M.; Sadeghpour, A.
CORPORATE SOURCE: Department of Biochemistry and Molecular Pathology, Northeastern Ohio Universities College of Medicine, Rootstown, OH, 44272-0095, USA
SOURCE: Falk Symp. (1999), 108(Bile Acids and Cholestasis), 51-58
CODEN: FASYDI; ISSN: 0161-5580
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 9
REFERENCE(S): (1) Chiang, J; J Biol Chem 1994, V269, P17502 CAPLUS
(2) Crestani, M; J Lipid Res 1998, V39, P2192 CAPLUS
(3) Forman, B; Cell 1995, V81, P687 CAPLUS
(6) Peet, D; Cell 1998, V93, P693 CAPLUS
(8) Stroup, D; Am J Physiol 1997, V273, PG508 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB The aim of the study was to identify the transcription factors bound to regulatory elements in CYP7A **gene** by DNase I footprinting, transient transfection assays of promoter/**reporter** chimeric

genes, and EMSA assays. A human liver cDNA expression library was **screened** with an oligonucleotide probe contg. BARE-II for DNA binding proteins. DNA binding proteins were partially purified using DNA affinity column chromatog. It was found that orphan **nuclear receptors** COUP-TFII, HNF4 and LXR are able to bind to BARE sequences and regulate CYO7A **gene** transcription. Potential role of these **nuclear receptors** in down-regulation of CYP7A **gene** transcription by bile acids were also studied.

L8 ANSWER 31 OF 42 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:617383 CAPLUS
TITLE: Discovery of novel modulators of the peroxisome proliferator-activated receptor g using combinatorial chemistry.
AUTHOR(S): Collins, Jon L.; Holmes, Christopher P.; Blanchard, Steven G.; Cobb, Jeffery E.; Cooper, Joel P.; Goreham, Donna M.; Hull-Ryde, Emily A.; Kliewer, Steven A.; Lehmann, Jurgen M.; Lenhard, James M.; Miller, Ann B.; Mohr, Christopher P.; Moore, Linda B.; Oberfield, Jennifer L.; Parks, Derek J.; Plunket, Kelli D.; Xu, Eric; Milburn, Michael V.; Willson, Timothy M.
CORPORATE SOURCE: Glaxo Wellcome Research and Development, Research Triangle Park, NC, 27709, USA
SOURCE: Book of Abstracts, 218th ACS National Meeting, New Orleans, Aug. 22-26 (1999), MEDI-012. American Chemical Society: Washington, D. C.
CODEN: 67ZJA5
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB The peroxisome proliferator-activated receptors (PPARs) are **ligand**-activated transcription factors that belong to the **nuclear receptor** superfamily. PPARs regulate the expression of **genes** whose protein products are involved in glucose and lipid homeostasis. During our **screening** efforts directed towards the identification of novel **ligands** for the PPAR gamma subtype (PPARg), we discovered a partial agonist (GW8647) of PPARg from a combinatorial library of 9,760 thiazolidinones. Intrigued by the functional profile of GW8647, addnl. focused libraries were synthesized using solid-phase parallel array synthesis. From these libraries GW0072 was identified as a high affinity (K.ident.70 nM) PPARg **ligand** that shows low efficacy in a **reporter gene** assays, blocks the adipogenic activity of a full agonist of PPARg in cell culture, and displays a novel mechanism of **nuclear receptor** antagonism. The application of split-mix solid-phase chem., serial deconvolution, parallel array synthesis, and structure-based library design to the discovery of GW0072 will be discussed.

L8 ANSWER 32 OF 42 USPATFULL
ACCESSION NUMBER: 1998:78949 USPATFULL
TITLE: Method of identifying negative hormone and/or antagonist activities
INVENTOR(S): Klein, Elliott S., Marina Del Rey, CA, United States
Nagpal, Sunil, Lake Forest, CA, United States
Chandraratna, Roshantha A., Mission Viejo, CA, United States
PATENT ASSIGNEE(S): Allergan, Inc., Irvine, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5776699		19980707	
APPLICATION INFO.:	US 1996-613863		19960311	(8)

DOCUMENT TYPE: Utility

FILE SEGMENT: Granted
PRIMARY EXAMINER: Walsh, Stephen
ASSISTANT EXAMINER: Sorensen, Kenneth A.
LEGAL REPRESENTATIVE: Knobbe, Martens, Olson & Bear
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 30 Drawing Figure(s); 15 Drawing Page(s)
LINE COUNT: 6510
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD Our method of RAR negative hormone **screening** based on the use of CV-1 cells co-transfected with the ERE-tk-Luc luciferase **reporter** plasmid and the ER-RXR-.alpha. and RAR-.gamma.-VP-16 receptor expression plasmids can be adapted generally such that the RAR-.gamma. moiety of the. . . to that of peroxisome proliferator-activated receptors (PPAR), vitamin D receptor (VDR), thyroid hormone receptor (T3R) or any other steroid superfamily **nuclear receptor** capable of heterodimerizing with RXR. CV-1 cells co-transfected with such plasmids would express high basal levels of luciferase activity. **Ligands** capable of binding the **ligand** binding domain of the receptor substituted for the RAR-.gamma. moiety can be easily **screened** for negative hormone activity by measuring their ability to repress luciferase activity.
DETD For steroid superfamily **nuclear receptors** that do not heterodimerize with RXR (e.g., glucocorticoid and estrogen receptors) the same end result can be achieved using GR-VP-16 or ER-VP-16 receptors and a luciferase **reporter** plasmid consisting of the appropriate glucocorticoid or estrogen response element fused to a heterologous promoter element and luciferase or other **reporter gene**. An essential feature of a generalized negative hormone **screening** assay is the inclusion of at least the **ligand** binding domain of the particular **nuclear receptor** for which inverse agonists are to be **screened** and a method for localizing the **nuclear receptor ligand** binding domain to the promoter of a **reporter gene**. This could be achieved using the receptors's natural DNA binding site, or alternatively by construction of a chimeric receptor having a heterologous DNA binding domain and corresponding use of a **reporter gene** which is under control of a DNA regulatory element which is recognized by the heterologous DNA binding domain. In a preferred embodiment, the plasmid expressing the **nuclear receptor** for which inverse agonists are to be **screened** would express this **nuclear receptor** as a fusion protein containing a constitutive activation domain, such as the HSV VP-16 activation domain, in order to provide allow high basal activity. This high basal activity would effectively increase assay sensitivity, thereby allowing analysis of **nuclear receptor ligands** which repress basal transcriptional activity in the absence of added **nuclear receptor** agonist.

L8 ANSWER 33 OF 42 MEDLINE
ACCESSION NUMBER: 1998409626 MEDLINE
DOCUMENT NUMBER: 98409626 PubMed ID: 9736705
TITLE: Ciona intestinalis nuclear receptor 1: a member of steroid/thyroid hormone receptor family.
AUTHOR: Carosa E; Fanelli A; Ulisse S; Di Lauro R; Rall J E; Jannini E A
CORPORATE SOURCE: Department of Experimental Medicine, University of L'Aquila, 67100 L'Aquila, Italy.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1998 Sep 15) 95 (19) 11152-7. Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF077403
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 19990106
Entered Medline: 19981026

AB Nuclear hormone receptors comprise a large family of zinc finger transcription factors, some with hydrophobic **ligands**, such as thyroid hormone, vitamin D, steroids, etc., and others for which no **ligand** has been found. Thyroid hormone receptors (TRs) generally are considered to be confined to the vertebrata that possess a thyroid.

. hormone in their metamorphosis, but no data are available on TRs in this genus; hence, we have studied Ciona intestinalis. **Screening** of a Ciona library with the DNA binding domain of Xenopus laevis TR (xTR) resulted in the isolation of a nuclear hormone receptor, C. intestinalis **nuclear receptor** 1 (CiNR1). CiNR1 is similar to TRs of more evolved species with a conserved DNA binding domain whereas the **ligand** binding domain shows poor homology to vertebrate sequences. The C-terminal part of CiNR1 spans approximately 200 amino acids more than. . . AF2 transactivation domain, and is not able to bind triiodothyronine. Phylogenetically, CiNR1 appears to be close to the common ancestral **gene** of TRs. Expression of CiNR1 was limited to the developing embryo and the larval stage, which suggests a role during development and metamorphosis. In transfection experiments, CiNR1 down-regulated basal transcription of a **reporter gene** driven by the TR palindrome responsive element. When CiNR1 was cotransfected with chicken TRalpha, it attenuated the normal thyroid hormone. . .

L8 ANSWER 34 OF 42 MEDLINE
ACCESSION NUMBER: 1999081323 MEDLINE
DOCUMENT NUMBER: 99081323 PubMed ID: 9865725
TITLE: Modulation of aromatase expression in the breast tissue by ERR alpha-1 orphan receptor.
AUTHOR: Yang C; Zhou D; Chen S
CORPORATE SOURCE: Division of Immunology, Beckman Research Institute of the City of Hope, Duarte, California 91010, USA.
CONTRACT NUMBER: CA 65767 (NCI)
CA44735 (NCI)
SOURCE: CANCER RESEARCH, (1998 Dec 15) 58 (24) 5695-700.
Journal code: CNF; 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990209
Last Updated on STN: 19990209
Entered Medline: 19990125

AB We have previously identified a silencer element (S1) that is situated between promoters I.3 and II of the human aromatase **gene** and that down-regulates the action of these promoters. We recently applied the yeast one-hybrid approach to **screen** a human breast tissue hybrid cDNA expression library for **genes** encoding the proteins binding to the silencer region. Most proteins identified from this approach belong to the **nuclear receptor** superfamily. Fifty % of the positive clones encode for ERR alpha-1, and other positive clones include EAR-2, EAR-3 (COUP-TF1), RAR. . . interacting with S1, we decided to examine the regulatory action of ERR alpha-1 on promoter I.3 of the human aromatase **gene**. Using a **reporter** plasmid that includes the aromatase genomic fragment containing promoter I.3 and S1, ERR alpha-1

was found to have a positive. . . 96 and 107 bp relative to the transcriptional start site of promoter I.3. In addition, despite the fact that the **nuclear receptor** SF1 was shown previously to bind to the same site and to mediate a cAMP response in ovary, our yeast one-hybrid **screening** did not find any SF-1 clones. Gel mobility shift assays further revealed that SF-1 can bind to the silencer element. . . nuclear proteins interacting with S1 in breast cancer tissue. It is thought that the silencer element in the human aromatase **gene** may function differently in different tissues because of distinct expression patterns of transcription factors.

L8 ANSWER 35 OF 42 MEDLINE
ACCESSION NUMBER: 95198733 MEDLINE
DOCUMENT NUMBER: 95198733 PubMed ID: 7891708
TITLE: The orphan receptor hepatic nuclear factor 4 functions as a transcriptional activator for tissue-specific and hypoxia-specific erythropoietin gene expression and is antagonized by EAR3/COUP-TF1.
AUTHOR: Galson D L; Tsuchiya T; Tendler D S; Huang L E; Ren Y; Ogura T; Bunn H F
CORPORATE SOURCE: Department of Medicine, Brigham & Women's Hospital, Boston, Massachusetts 02115.
CONTRACT NUMBER: RO1-DK41234 (NIDDK)
RO1-GM26444 (NIGMS)
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (1995 Apr) 15 (4) 2135-44. Journal code: NGY; 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-L16588
ENTRY MONTH: 199504
ENTRY DATE: Entered STN: 19950427
Last Updated on STN: 19990129
Entered Medline: 19950420

AB The erythropoietin (Epo) **gene** is regulated by hypoxia-inducible cis-acting elements in the promoter and in a 3' enhancer, both of which contain consensus hexanucleotide hormone receptor response elements which are important for function. A group of 11 orphan **nuclear receptors**, transcribed and translated in vitro, were **screened** by the electrophoretic mobility shift assay. Of these, hepatic nuclear factor 4 (HNF-4), TR2-11, ROR alpha 1, and EAR3/COUP-TF1 bound. . . Transfection of a plasmid expressing HNF-4 into HeLa cells enabled an eightfold increase in the hypoxic induction of a luciferase **reporter** construct which contains the minimal Epo enhancer and Epo promoter, provided that the nuclear hormone receptor consensus DNA elements in. . . the DNA binding domain of HNF-4 but lacks the C-terminal activation domain. Moreover, the hypoxia-induced expression of the endogenous Epo **gene** was significantly inhibited in Hep3B cells stably transfected with HNF-4 delta C. On the other hand, cotransfection of EAR3/COUP-TF1 and the Epo **reporter** either with HNF-4 into HeLa cells or alone into Hep3B cells suppressed the hypoxia induction of the Epo **reporter**. These electrophoretic mobility shift assay and functional experiments indicate that HNF-4 plays a critical positive role in the tissue-specific and hypoxia-inducible expression of the Epo **gene**, whereas the COUP family has a negative modulatory role.

L8 ANSWER 36 OF 42 MEDLINE
ACCESSION NUMBER: 96192924 MEDLINE
DOCUMENT NUMBER: 96192924 PubMed ID: 8614404
TITLE: TOR: a new orphan receptor expressed in the thymus that can modulate retinoid and thyroid hormone signals.

AUTHOR: Ortiz M A; Piedrafita F J; Pfahl M; Maki R
CORPORATE SOURCE: La Jolla Cancer Research Foundation, California 92037, USA.
SOURCE: MOLECULAR ENDOCRINOLOGY, (1995 Dec) 9 (12) 1679-91.
Journal code: NGZ; 8801431. ISSN: 0888-8809.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U39071
ENTRY MONTH: 199606
ENTRY DATE: Entered STN: 19960613
Last Updated on STN: 19960805
Entered Medline: 19960603

AB . . . of vitamin A, retinoic acid, as well as vitamin D3 and thyroid hormones exert their actions by binding to specific **nuclear receptors** that represent one subfamily of the steroid/thyroid hormone receptor superfamily. To identify new members of the retinoid/thyroid hormone receptor subfamily that could play a role in the immune system, a **screening** of a T cell cDNA library was performed using a retinoid X receptor probe. A clone was isolated encoding a novel **nuclear receptor** expressed mainly in the thymus and T cell line s. This new receptor, TOR (thymus orphan receptor), is most closely related in both its DNA-binding domain and **ligand**-binding domain, 90% and 53%, respectively, to ROR alpha/RZR alpha and clusters with these two receptors and RZR beta in a phylogenetic tree, when both the DNA-binding domain and the **ligand**-binding domain sequences of **nuclear receptors** are compared. Thus, TOR is part of a subgroup of receptors, one of which has recently been reported to be. . . binding sites for thyroid hormone (TR), and retinoic acid receptors (RAR). In transient transfection experiments TOR does not activate a **reporter gene** carrying these sequences in the absence or the presence of any known **nuclear receptor ligands**. TOR, however, is able to repress TR and RAR activity on DR-4-TREs or DR-5-RAREs, respectively. Therefore, our data suggest that. . .

L8 ANSWER 37 OF 42 MEDLINE
ACCESSION NUMBER: 95166235 MEDLINE
DOCUMENT NUMBER: 95166235 PubMed ID: 7862143
TITLE: Genetic dissection of thyroid hormone receptor beta: identification of mutations that separate hormone binding and transcriptional activation.
AUTHOR: Uppaluri R; Towle H C
CORPORATE SOURCE: Department of Biochemistry, University of Minnesota, Minneapolis 55455.
CONTRACT NUMBER: 5T32-GM07323 (NIGMS)
DK39997 (NIDDK)
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (1995 Mar) 15 (3) 1499-512.
Journal code: NGY; 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199503
ENTRY DATE: Entered STN: 19950404
Last Updated on STN: 19950404
Entered Medline: 19950323

AB The thyroid hormone receptors (TR) are members of the **nuclear receptor** family of **ligand**-mediated transcription factors. The large region of TR that lies C-terminal to its DNA-binding domain subserves functions of **ligand** binding, dimerization, and transactivation. Little is known regarding the structural or functional

determinants of these processes. We have utilized genetic **screening** in the yeast Saccharomyces cerevisiae to identify residues involved in these functions. Random mutations of the rat TR beta 1 isoform between amino acid residues 179 and 456 were **screened**, and mutants with reduced hormone-dependent activation of **reporter gene** activity were isolated. In this paper we describe the characterization of a class of mutants that exhibit a dissociation between. . . binding and transcriptional activation. These mutants retained hormone binding (> 15% of the wild-type level) yet failed to transactivate a **reporter gene**. A number of these mutations occurred within the D region, which links the DNA-binding and **ligand**-binding domains of the receptor. One subset of these mutations abrogated DNA binding, supporting a role of the D region in. . . mutations localized to the carboxy-terminal portion of the receptor in a region which contains elements conserved across the superfamily of **nuclear receptors**. The hormone-dependent phenotype of these superactivator mutations suggests an important role of this segment in **ligand**-mediated transcriptional activation.

L8 ANSWER 38 OF 42 MEDLINE
ACCESSION NUMBER: 96062010 MEDLINE
DOCUMENT NUMBER: 96062010 PubMed ID: 7488247
TITLE: Functional analysis of aryl hydrocarbon receptor nuclear translocator interactions with aryl hydrocarbon receptor in the yeast two-hybrid system.
AUTHOR: Yamaguchi Y; Kuo M T
CORPORATE SOURCE: Department of Molecular Pathology, University of Texas M.D. Anderson Cancer Center, Houston 77030, USA.
CONTRACT NUMBER: CA55813 (NCI)
CA55846 (NCI)
SOURCE: BIOCHEMICAL PHARMACOLOGY, (1995 Oct 12) 50 (8) 1295-302.
Journal code: 9Z4; 0101032. ISSN: 0006-2952.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199512
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19970203
Entered Medline: 19951214

AB The aryl hydrocarbon receptor (AHR) mediates dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin)-induced transcriptional activation of a battery of **genes** by interaction with a cofactor, called aryl hydrocarbon **receptor nuclear** translocator (ARNT) protein. Both AHR and ARNT belong to a family of proteins that includes the Drosophila circadian-rhythm protein and. . . yeast two-hybrid system with the N-terminal half of AHR as a probe, which contains the bHLH and PAS regions, to **screen** cDNA libraries prepared from human lymphocytes and C57BL mouse liver for clones encoding proteins capable of binding to these regions,. . . containing the GAL4 DNA binding domain (DB) linked to the full-length AHR was not capable of activating expression of a **reporter gene** containing the GAL4 DNA binding site, suggesting that **ligand**-free AHR alone has no transactivating properties in yeast. However, the C-terminal portion (amino acid residues 580-797) of the AHR, including the Q-rich domain, could confer transactivation of the **reporter gene** expression in the same system, suggesting that the N-terminal portion of the AHR contains transcription repression properties. In contrast, GAL4(DB)-ARNT fusion protein was able to activate expression of the same **reporter gene**. Deletion analysis of ARNT revealed that the C-terminal 75 amino acids, including the Q-rich domain, exhibited full transactivation function in. . .

L8 ANSWER 39 OF 42 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:487761 CAPLUS
DOCUMENT NUMBER: 123:2402
TITLE: Assignment of the human ubiquitous receptor gene (UNR)
to 19q13.3 using fluorescence in situ hybridization
AUTHOR(S): Le Beau, Michelle M.; Song, Ching; Davis, Elizabeth M.; Hiipakka, Richard A.; Kokontis, John M.; Liao, Shutsung
CORPORATE SOURCE: Dep. Med., Univ. Chicago, Chicago, IL, 60637, USA
SOURCE: Genomics (1995), 26(1), 166-8
CODEN: GNMCEP; ISSN: 0888-7543
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We recently cloned the human and rat cDNAs for a new member of the **nuclear receptor** family, which we named ubiquitous receptor (UR) because ofits expression in many tissues. The symbol for this **gene** is UNR (ubiquitous **nuclear receptor**). UR is a 50-kDa nuclear protein that belongs to the thyroid hormone/retinoic acid receptor subfamily of **nuclear receptors**, based on the P-box amino acids of its DNA-binding domain and its ability to bind to AGGTCA direct repeats with four-nucleotide (DR4) spacing as a heterodimer with RXR. In the absence of 9-cis-retinoic acid, coexpression of UR in combination with RXR in COS-1 cells stimulated a **reporter gene** contg. a DH4 response element. It is not known whether a **ligand** is required for UR function. Coexpression of UR inhibited RAR and RXR activation of DR4-linked **reporter gene** expression, but not a DR5-linked **reporter gene**, in the presence of all-trans-retinoic acid. Since UR can modulate the retinoid and thyroid hormone signaling pathways, it may have an important role in normal growth and differentiation. Human UNR cDNAs were used to **screen** a Lambda FIX II human male placenta genomic library (Stratagene). Phage DNA from clones hybridizing to UNR cDNA was characterized by Southern hybridization and restriction mapping, and two different clones (hG10 and hG12) with inserts of 15-20 kb were chosen for fluorescence in situ hybridization (FISH) anal. Biotin-labeled probes were prepd. from phage DNA by nick-translation using Bio-11-dUTP (Enzo Diagnostics). FISH was performed as described previously. Hybridization was detected with fluorescein-conjugated avidin (Vector Labs.), and chromosomes were identified by staining with 4,6-diamidino-2-phenylindole-dihydrochloride (DAPI). Hybridization of the UNR probe to normal human metaphase chromosomes resulted in specific labeling only of chromosome 19. Specific labeling of 19q13 was obsd. on four (14 cells), three (6 cells), two (4 cells), or one (1 cell) chromatid(s) of the chromosome 19 homologs in 25 cells examd. Of 85 signals obsd. (83 of 100 19q chromatids from 25 metaphase cells were labeled), 83 (97.6%) were located at 19q13.3. The remaining 2 signals were located at 17q25 (2.4%). Specific labeling of 19q13.3 was obtained in an addnl. hybridization expt. using the hG10 probe and in other hybridizations using another probe (hG12) for this **gene**. These results indicate that the UNR **gene** is localized to chromosome 19q13.3.

L8 ANSWER 40 OF 42 MEDLINE
ACCESSION NUMBER: 95140028 MEDLINE
DOCUMENT NUMBER: 95140028 PubMed ID: 7838156
TITLE: Identification of RVR, a novel orphan nuclear receptor that acts as a negative transcriptional regulator.
AUTHOR: Retnakaran R; Flock G; Giguere V
CORPORATE SOURCE: Division of Endocrinology, Hospital for Sick Children,

Toronto, Canada.
SOURCE: MOLECULAR ENDOCRINOLOGY, (1994 Sep) 8 (9) 1234-44.
Journal code: NGZ; 8801431. ISSN: 0888-8809.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U12142
ENTRY MONTH: 199502
ENTRY DATE: Entered STN: 19950314
Last Updated on STN: 19950314
Entered Medline: 19950227

AB A novel member of the steroid/thyroid/retinoid superfamily of **nuclear receptors** has been isolated as part of a **screen** to identify **genes** related to the recently characterized orphan receptor ROR alpha. This new orphan receptor, cloned from a mouse brain cDNA library, is closely related to the rat Rev-ErbA alpha **gene** product (97% and 68% identity in the DNA- and **ligand**-binding domains, respectively) and referred to as RVR. Northern blot analysis reveals that two RVR mRNA species are expressed during mouse. . . . it binds the DNA sequence ATAACTAGGTCA, a hormone response element composed of a 6-base pair AT-rich sequence preceding a single **nuclear receptor** recognition half-site core motif PuGGTCA. We show that RVR recognizes this hormone response element with a specificity similar to that. . . . 2. However, cotransfection studies indicate that RVR does not activate transcription when this hormone response element is linked to a **reporter gene** but rather acts as a potent competitive repressor of ROR alpha function. These results indicate the existence of an orphan **nuclear receptor**-based signaling pathway with the intrinsic ability to regulate the expression of specific **gene** networks through competition between transcriptional activators and repressors for the same recognition site.

L8 ANSWER 41 OF 42 MEDLINE
ACCESSION NUMBER: 93232045 MEDLINE
DOCUMENT NUMBER: 93232045 PubMed ID: 8473329
TITLE: RNR-1, a nuclear receptor in the NGFI-B/Nur77 family that is rapidly induced in regenerating liver.
AUTHOR: Scearce L M; Laz T M; Hazel T G; Lau L F; Taub R
CORPORATE SOURCE: Department of Genetics, Howard Hughes Medical Institute, University of Pennsylvania School of Medicine, Philadelphia 19104-6145.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1993 Apr 25) 268 (12) 8855-61.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-L08595
ENTRY MONTH: 199305
ENTRY DATE: Entered STN: 19930604
Last Updated on STN: 19980206
Entered Medline: 19930514

AB . . . hepatectomy provides one of the few systems for analysis of mitogenesis in the fully developed, intact animal. Immediate-early growth response **genes**, induced in the absence of prior protein synthesis, play an important regulatory role in the regenerative process. During **screening** of a subtracted cDNA library of immediate-early **genes** induced during liver regeneration, a novel member of the thyroid/steroid receptor superfamily, RNR-1 (regenerating liver **nuclear receptor**), was identified. This **gene** is not expressed in quiescent liver but is rapidly induced following

partial hepatectomy and is specific to hepatic growth as. . . in vitro translation in reticulocyte lysate. RNR-1 is highly homologous to r-NGFI-B/m-Nur77 particularly in the DNA binding (94%) and putative **ligand** binding (59%) domains. Using a mobility shift assay, we have shown that RNR-1 specifically binds to the NGFI-B DNA half-site. . . A box region important in mediating half-site binding is 100% conserved between r-NGFI-B/m-Nur77. Both RNR-1 and Nur77 strongly transactivate a **reporter** driven by a consensus r-NGFI-B/Nur77 binding site, and their effect together is additive. As both the RNR-1 and r-NGFI/m-nur77 **genes** are induced during liver regeneration, it is very possible that RNR-1 acts concomitantly with r-NGFI/m-Nur77 in regulating the expression of delayed-early **genes** during liver regeneration.

L8 ANSWER 42 OF 42 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1994:76103 BIOSIS
DOCUMENT NUMBER: PREV199497089103
TITLE: Genetic approaches to mammalian nuclear receptor function in yeast.
AUTHOR(S): Garabedian, Michael J.
CORPORATE SOURCE: Dep. Microbiol., NYU Med. Cent., New York, NY 10016 USA
SOURCE: Methods (Orlando), (1993) Vol. 5, No. 2, pp. 138-146. ISSN: 1046-2023.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Mammalian **nuclear receptor** function can be faithfully reconstituted in yeast, enabling a wide variety of genetic approaches to be taken toward defining the mechanisms of signal transduction and transcriptional regulation. This report describes vectors for the expression of mammalian receptors in yeast, **reporter genes**, yeast host strains, and simple assays that monitor receptor transcriptional activity. Methods for the generation of receptors with distinct defects in particular functions, such as DNA or hormone binding, that couple random mutagenesis with phenotypic **screens** are outlined as well. In addition, strategies for the identification of nonreceptor components whose **gene** products may act on receptors are discussed. The experimental advantages of yeast invite a detailed genetic analysis of mammalian **nuclear receptor** functions sbd hormone and DNA binding, nuclear localization, and interaction with nonreceptor factors sbd and should illuminate further the mechanisms. . .

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